UNITED STATES DISTRICT COURT
WESTERN DISTRICT OF TENNESSEE
WESTERN DIVISION

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| MICHELLE MOBLEY, et al. | ) | CIVIL ACTION NO. 2:13-cv-02985-JTF-cgc |
| | ) | 2:13-cv-02865-JTF-cgc |
| Plaintiffs | ) | 2:13-cv-02869-JTF-cgc |
| | ) | 2:13-cv-02871-JTF-cgc |
| v. | ) | 2:13-cv-02873-JTF-cgc |
| | ) | 2:13-cv-02883-JTF-cgc |
| MEDTRONIC, INC.; and | ) | 2:13-cv-02866-JTF-cgc |
| MEDTRONIC SOFAMOR | ) | 2:13-cv-02868-JTF-cgc |
| DANEK USA, INC., | ) | 2:13-cv-02861-JTF-cgc |
| | ) | 2:13-cv-02870-JTF-cgc |
| Defendants | ) | 2:13-cv-02872-JTF-cgc |
| | ) | 2:14-cv-02196-JTF-cgc |
| | ) | 2:13-cv-02340-JTF-dkv |
| | ) | 2:13-cv-02341-JTF-dkv |
| | ) | 2:13-cv-02342-JTF-cgc |
| | ) | 2:13-cv-02343-JTF-dkv |
| | ) | 2:13-cv-02344-JTF-tmp |
| | ) | 2:13-cv-02345-JTF-dkv |
| | ) | 2:13-cv-02346-JTF-cgc |
| | ) | 2:13-cv-02347-JTF-tmp |
| | ) | 2:13-cv-02348-JTF-dkv |
| | ) | 2:13-cv-02349-JTF-tmp |
| | ) | 2:13-cv-02350-JTF-dkv |
| | ) | 2:13-cv-02351-JTF-tmp |
| | ) | 2:13-cv-02396-JTF-dkv |
| | ) | 2:13-cv-02433-JTF-dkv |
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| | ) | 2:13-cv-02644-JTF-dkv |
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| | ) | 2:13-cv-02699-JTF-tmp |
| | ) | 2:13-cv-02706-JTF-dkv |
| | ) | 2:13-cv-02709-JTF-dkv |
| | ) | 2:13-cv-02783-JTF-tmp |
| | ) | 2:13-cv-02862-JTF-cgc |
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**MASTER COMPLAINT AND DEMAND FOR JURY TRIAL AGAINST MEDTRONIC DEFENDANTS**

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COME NOW, Plaintiffs in the above-styled actions, collectively, by and through the counsel, and pursuant to this Court's Order, file this *MASTER COMPLAINT AND DEMAND FOR JURY TRIAL* against Defendants MEDTRONIC, INC. ("Medtronic") and MEDTRONIC SOFAMOR DANEK USA, INC. ("MSD") as an administrative device to set forth potential claims Plaintiffs, on their own behalf and/or on behalf of the estates of deceased persons and their beneficiaries, may assert against these Defendants in this litigation. Hereafter, Medtronic and MSD collectively are called "the Medtronic Defendants." Allegations pled herein are deemed pled in any previously-filed case pending in this Court, and in all future related cases adopting this Master Complaint, and Plaintiff-specific allegations in individual Complaints already filed of record are incorporated herein by reference.

## I. PARTIES

1. Plaintiffs are all individuals, along with their spouses (if any), who suffered injuries as a result of their exposure to components or individual parts of Medtronic's Infuse® Bone Graft/LT-Cage™ Lumbar Tapered Fusion Device (Infuse®).

2. Defendant MEDTRONIC, INC. is a Minnesota corporation, with its principal place of business at 710 Medtronic Parkway, Minneapolis, Minnesota 55432.

3. Defendant MEDTRONIC SOFAMOR DANEK USA, INC. ("MSD") is a Tennessee corporation, with its principal place of business at 2600 Sofamor Danek Drive,

Memphis, Tennessee 38132. Defendant MSD is a wholly owned subsidiary of Defendant Medtronic.

## II. JURISDICTION AND VENUE

4. This Court has personal jurisdiction over Defendants because at all relevant times they have engaged in substantial business activities and/or resided in the State of Tennessee in Shelby County. At all relevant times, the Defendants transacted, solicited, and conducted business in the State of Tennessee through their employees, agents and/or sales representatives, and derived substantial revenue from such business in the State of Tennessee.

5. This Court has personal jurisdiction over Medtronic under Tenn. Code Ann. §20-2-201 and §20-2-14 *et seq.* (the Long Arm Statutes) as this Defendant has systematically and continuously transacted business in this state, either itself or through the control of its subsidiaries, and supplied their products in this state.

6. Venue over all the Defendants is proper in Shelby County the Defendants reside, do business in and/or are headquartered in Shelby County and specifically because the Medtronic Defendants have had substantial, systematic, and continuous contacts with the State of Tennessee in Shelby County. Damages in this case are in excess of the jurisdictional limits of this Court and of the United States District Court; however, no diversity of citizenship exists between the parties herein pursuant to 28 U.S.C. § 1332.

## III. OVERVIEW OF CASE.

### A. PLAINTIFFS' UNDERWENT SPINAL FUSION SURGERY WITH FUSION CAGES.

7. Plaintiffs all underwent some type of spinal fusion procedure between 2002 through 2013.[1] The surgeries were generally performed because of severe back pain.

[1] Specific facts related to each individual Plaintiff's procedure can be found in the separate complaints filed in the individual actions.

8. In the vast majority of Plaintiffs' surgeries, a surgical intervertebral fusion cage was inserted between the vertebrae into one or more levels of the spine from a posterior approach (an incision in the back or side of the patient).

9. These fusion cages were used to spread the vertebrae apart, making the openings in the back of the spine larger and allowing more room for nerve roots, to decrease pinching and irritation on the nerves.

10. Also, these fusion cages are used to replace ruptured or deviated discs between the vertebrae which may be impinging on the spine.

11. Generally, these cages increase stability between the two vertebrae by allowing bone to grow between them so that the vertebrae become "fused" together.

12. This increase in space between vertebrae and fusion between the vertebrae should eliminate mechanical movement between the vertebrae, thus relieving back pain by reducing irritation and impingement on nerves.

13. The fusion cages used in Plaintiffs' surgeries (hereafter called "P's Cages") were approved for use with the patients' own bone (or bone from a cadaver) to create a bone graft bridge between vertebrae.

14. Usually, when the patients' own bone is used, it is obtained either from the surgical site or other areas of the body, like the hip.

15. Bone placed in the fusion cages causes bone between vertebrae to grow and "weld" them together, thus hopefully increasing stability and decreasing pressure and irritation on the spinal cord and nerve roots.

### B. P'S CAGES WERE FILLED WITH THE BMP SPONGE, THE 1ST COMPONENT OF A COMBINATION BIOLOGIC/DEVICE CALLED "INFUSE®." FDA APPROVED INFUSE® TO BE USED AS A "SINGLE ENTITY" WITH TWO COMPONENTS.

16. Contrary to their design and FDA approvals, P's Cages were not filled solely with

Plaintiffs' own bone (or bone from a cadaver).

17. P's Cages were packed with a bio-engineered and bio-manufactured bone-growth material known as Bone Morphogenetic Protein ("BMP"), which is typically soaked into a collagen sponge (BMP/Sponge).

18. The BMP/Sponge was approved for marketing by the Federal Food and Drug Administration ("FDA") for use in spinal fusion procedures, but ***only*** as the 1st of a 2 component (3 part) medical device called "Infuse® Bone Graft/LT-Cage™ Lumbar Tapered Fusion Device" (Infuse®).

19. To be safe and effective, the BMP/Sponge (parts 1 and 2) was to be inserted into the 2nd Component, the "LT-CAGE™ (part 3), which is a hollow titanium cylinder designed to prevent excess bone growth which may cause damage to the nerve roots and spinal cord.

**1. A Short History of BMP and MSD's Clinical Trials.**

20. Medtronic's subsidiary, Medtronic Sofamor Danek, Inc. ("MSD"), first bought a license to use Bone Morphogenetic Protein ("BMP") from Genetics Institute, Inc. (a subsidiary of Wyeth) on February 16, 1995. The patent on BMP describes it as a purified protein used for the treatment of bone and cartilage defects.[2]

21. In October, 1996, MSD obtained an Investigational Device Exemption (IDE) to begin clinical studies of BMP for the purpose of growing bone between vertebrae to be used in spine fusion surgeries.

22. If successful, MSD hoped BMP would eliminate the need to use the patient's own bone (usually taken from the hip) and/or cadaver bone to stimulate bone growth.

23. MSD clearly anticipated that BMP would be used in all types of common spine

[2] http://www.patentstorm.us/patents/5618924.html (for a description of the patent, applied for on 3/19/91 and issued April 8, 1997.)

fusion surgery, resulting in massive sales potential.

24. But in 1999, one part of MSD's IDE clinical trial was halted when 75% of exposed patients undergoing "posterior" approach surgery (incisions from the back) grew excess bone into their spinal canal potentially causing failed surgeries or increased disabilities and pain.

25. Based on the results of its own clinical trials, MSD could prove to the FDA that the BMP/Sponge was safe and effective for ***only a very limited*** type of surgery, known as an Anterior Lumbar Interbody Fusion (ALIF), and then only when used through a specifically designed fusion cage for that purpose, called the "LT-CAGE™.

26. According to the clinical studies submitted to the FDA by Medtronic, the BMP/Sponge was safe and effective only when it was implanted through an incision into the stomach and implanted in the front of the spine. Also, this implantation could only occur in one level of the "lumbar" (lower back) portion of the spine.

27. MSD therefore applied to the FDA for a Premarket Approval ("PMA") of BMP restricted to a very small subset of spine fusion surgeries.

**2. The FDA Restricted BMP's Use and Route of Administration.**

28. On July 2, 2002, MSD obtained from the FDA a Pre-Market Approval ("PMA") for Infuse® Bone Graft/LT-Cage™ Lumbar Tapered Fusion Device as a single Class III device.

29. FDA separates medical devices into three classes, with Class III devices receiving the highest degree of scrutiny from the FDA because these devices may present the highest degree of risk.

30. In contrast to other combination medical devices, the BMP/sponge (separate from the other parts of Infuse®) is not classified and has never been tested or reviewed by FDA for marketing.

31. During the FDA Advisory Committee Panel ("FDA Panel") hearing on January 10, 2002 concerning potential FDA approval of Infuse®, panel members voiced concerns regarding use of the product.

32. They asked the Medtronic Defendants to describe their efforts to self-guard against uses of BMP and its components and parts which were not proven safe and effective by the clinical studies submitted for marketing approval by the Medtronic Defendants..

33. The FDA Panel members, such as Dr. John Kirkpatrick, cautioned the Medtronic Defendants to guard against procedures outside ALIF procedures shown to be safe and effective by clinical studies using the BMP/Sponge.

34. Dr. Kirkpatrick emphasized the need to use the two components of Infuse® together, because the LT-CAGE™ had been specifically designed for ALIF surgeries (through the front of the patient) and therefore would discourage the use of BMP in posterior approach surgeries (through the back of the patient).

35. The 2002 FDA approval restricted the use of Infuse® to ALIF procedures with an anterior approach to a single level spinal region from L4-S1.[3]

36. In 2004, the FDA approved a supplement expanding the "intended use" of Infuse® to include ALIF procedures with an anterior approach to the spinal region from L2-S1.

37. As explained in its labeling, the FDA's approval for Infuse® was limited, because "[t]he safety and effectiveness of…[the BMP/Sponge] with other spinal implants [***other than*** the

[3] The FDA approval letter specifically states, "[t]his device is indicated for spinal fusion procedures in skeletally mature patients with degenerative disc disease (DDD) at one level from L4-S1…InFUSE™ Bone Graft/LT -CAGE™ devices are to be implanted via an anterior open or an anterior laparoscopic approach," Letter from the FDA to Medtronic Vice President Richard Treharne, Ph.D. regarding PMA Approval (July 2, 2002), *available at* http://www.accessdata.fda.gov/cdrh_docs/pdf/P000058a.pdf (also attached hereto as Exhibit 1); *see also* Infuse® Label, "These components must be used as a system. The Infuse® Bone Graft component must not be used without the LT-Cage Lumbar Tapered Fusion Device component." *available at* http://www.accessdata.fda.gov/cdrh_docs/pdf/P000058c.pdf (also attached hereto as Exhibit 2).

LT-Cage™], implanted at locations ***other than*** the lower lumbar spine, or used in surgical techniques ***other than*** anterior…approaches ***[had]. . .not been established***."[4]

**3. Infuse® Was Not Used In Plaintiffs' Surgeries.**

38. The BMP/Sponge was designed to be inserted as "filler" into the 2nd Component of Infuse®, a fusion cage called the LT-Cage™.

39. The LT-Cage™ was designed and tested to be inserted through anterior approach surgeries (from an incision in the front of the patient).

40. Although the FDA approved as safe and effective the use of the BMP/Sponge together with the LT-Cage™ in anterior approach (from the front) surgeries, ***none*** of the Plaintiffs' surgeons used the LT-Cage™ in their surgery and the surgeries were ***not*** from an anterior approach.

41. Infuse® was defined by the FDA as a single medical device made up of a ***system*** of two components, the BMP/Sponge and the LT-Cage™, and was designed and tested by Defendants used together, with the BMP/Sponge inserted into the LT-Cage™.

42. In July, 2002, the sole FDA approved use of the BMP/Sponge was as a system of two components, in Infuse®. No other clinical tests were performed to demonstrate that the BMP/Sponge was safe and effective either used alone, or in combination with any other medical device. The FDA did not evaluate any other uses of the system.

43. Infuse® is therefore a "Device-Biologic"[5] "combination product."[6]

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[4] Exhibit 2, FDA Approved Labeling.

[5] *See "The Silver Sheet,"* Vol. 8, No. 11 (November 2004), a well-known industry newsletter, attached hereto as Exhibit 3, which described Infuse® as follows:

> The product consists of three main components: a metal spinal fusion cage; a genetically engineered human protein (rhBMP-2) in powder form; and a collagen sponge to carry the protein.
>
> The rhBMP-2 powder and collagen sponge are packaged together in a kit that also contains sterile water (used to mix the protein powder into a liquid solution) and a syringe. The metal cage device is packaged and sold separately.

44. A combination product has been very specifically defined in FDA regulations since 1991. Per the literal terms of the FDA's regulations, Infuse® is a "biologic/device…mixed…as a ***single entity***...."[7] (Emphasis added.)

45. As a combination product, the PMA for Infuse® only applies to the device when all three parts (comprising the two components) are used as a single entity.

46. BMP is defined by the FDA as a "therapeutic biologic."[8]

47. A "biologic" is defined by the Public Health Service Act.[9]

48. "Device" is defined by the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 301, *et seq*. (2012) (the "FDCA"), which includes the Medical Device Amendments of 1976.[10]

49. Drugs, devices and biologics are markedly different for purposes of FDA regulatory mechanisms, with different aspects of the FDA orchestrating their regulations.

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> The **combination product** was approved via PMA in 2002 for the treatment of degenerative disc disease in the lower spine. Surgeons soak the sponge with the rhBMP-2 solution and place it inside the cage; the cage is then implanted between the patient's vertebrae, where the rhBMP-2 promotes new bone growth to fuse the spine.

(Emphasis added.)

[6] *See*, PMA Approval for P000058 dated July 11, 2002 (Infuse Bone Graft/LT-Cage Lumbar Tapered Fusion Device), specifically designating Infuse® as a "Combination Device", attached hereto as Exhibit 4; *also available at* http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=13698 .

[7] 21 CFR §3.2(e), quoted below:

> (e) Combination product includes:
>
> (1) A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity;
>
> …
>
> (3) A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose;

[8] *See* "Guidance for Industry and FDA, Class II Special Controls Guidance Document: Intervertebral Body Fusion Device," attached hereto as Exhibit 5.

[9] The BMP in Infuse® is a "biological product" and "has the meaning given the term in section 351(a) of the Public Health Service Act *(42 U.S.C. 262*(a))." 21 CFR §3.2(d).

[10] 21 U.S.C. § 321(g) defines "device" for the purpose of the FDCA and FDA Regulations. 21 U.S.C. § 321(g) defines "drug" for the purposes of the FDCA and FDA Regulations.

50. As a biologic, BMP ordinarily would be governed by the FDA's Center for Drug Evaluation or Research ("CDER")[11] (if distributed separately from Infuse®).

51. In contrast, the Center for Devices and Radiological Health ("CDRH") orchestrates regulatory authority over all "devices" as defined in the FDCA.

52. BMP as a biologic likely would be FDA-approved for marketing, by itself, through the CDER via a New Drug Application ("NDA") or through a Biologics License Application ("BLA").[12]

53. The CDER has a Division of Therapeutic Protein (DRP) with regulatory responsibility for multiple biological therapeutics,[13] like BMP.[14]

54. Marketed separately, both the collagen sponge[15] and the LT-CAGE™[16] would be "devices" falling clearly under the jurisdiction of the CDRH.

55. The FDA's CDER never reviewed or approved BMP to be marketed as a biologic.

56. Neither the CDER nor the CDRH approved or reviewed the BMP/Sponge to be marketed separately intended for use in fusion surgeries in the lumbar spine, apart from the LT-

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[11] *See generally,* definitions in 21 CFR §3.2(b).

[12] http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/BiologicsLicenseApplicationsBLAProcess .

[13] *See, e.g.*, FDA's website discussing the CDER and its Office of Biotechnology Products (OBP): http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/default.htm and http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm090470.htm

[14] *See* Division of Therapeutic Proteins line chart, attached hereto as Exhibit 6. *See also,* list of approved biologic products attached hereto as Exhibit 7.

[15] The collagen sponge in Infuse® is a Class II medical device and classified separately as a resorbable calcium salt bone void filler device. *See,* "Guidance for Industry and FDA Staff – Class II Special Controls Guidance Document: Resorbable Calcium Salt Bone Void Filler Device," attached hereto as Exhibit 8.

[16] The LT-CAGE™ is now defined as a Class II "Intervertebral body fusion device." *See* 21 CFR 888.3080, attached as Exhibit 9. However, such devices are elevated to Class III when they "include any therapeutic biologic (e.g., bone morphogenic protein)." *Id.* Intervertebral body fusion devices were Class III until June, 2007, when the FDA downgraded them to Class II devices when using "autologous" bone grafts. *See* FDA Website: "Guidance for Industry and FDA Staff -- Class II Special Controls Guidance Document: Intervertebral Body Fusion Device," issued June 12, 2007, attached as Exhibit 10.

Cage™.

57. However, recognizing that the original Infuse® PMA would ***not*** apply, Medtronic did obtain new, separate PMAs for the BMP/sponge component alone, when intended to be used for repair of open tibia fractures and in some oral and sinus surgeries.[17]

58. For the purpose of the FDA's regulations, the components and parts of Infuse® (when used in spinal surgeries) cannot be treated separately because each such part is governed by a totally separate set of FDA regulations and as a combination product must be treated as a "***single entity***…."

59. Infuse®, as defined by the FDA PMA approval, was not used in any of Plaintiffs' fusion surgeries.

60. The Medtronic Defendants intended to and did deliver the BMP/Sponge separately to each of the Plaintiffs, to be used apart from the LT-Cage™.

61. According to the Infuse® PMA and FDA regulations, Infuse® was approved as a "system" and therefore a "single entity…" The approved labeling for Infuse® reads in part, with bold and underlined formatting: **"These components must be used as a system. The Infuse® Bone Graft component must not be used without the LT-Cage Lumbar Tapered Fusion Device component."**[18]

62. The separate components and parts of Infuse® are not Infuse®.[19] The Infuse® PMA requirements do not attach to these components when used separately, because these

[17] *See*, PMA Approval for P000054 dated April 30, 2004 (open tibial fractures), *available at* http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=18471 and attached hereto as Exhibit 11; and PMA Approval for P050053 dated March 13, 2007 (certain maxillofacial surgeries), *available at* http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=22658 and attached hereto as Exhibit 12.

[18] Infuse® Label, Exhibit 2.

[19] Even if the Infuse® PMA requirements somehow applied separately to its component parts (which they do not), the Medtronic Defendants intended to and did violate the restrictions of the Infuse® PMA to the various combinations of these biologic/devices outlined above, by promoting BMP use in posterior approach surgeries *without* the LT-Cage™.

components, when used separately, are a different and distinct biologic, and different and distinct devices.

### C. DEFENDANTS RECRUITED KEY OPINION LEADERS (KOLS) TO MARKET BMP, UNAPPROVED BY THE FDA, ALONE AND IN COMBINATIONS WITH VARIOUS DEVICES.

63. The vast majority of spinal fusion surgeries are "posterior" as opposed to the "anterior" approach approved by the FDA for Infuse®.

64. The FDA severely limited the sales market for BMP to being a part of Infuse® and then only "anterior" approach surgeries using the LT-CAGE™. But MSD's ambitions for sales were not so limited.

65. From the very beginning, MSD endeavored to expand BMP's market.

66. Sales of "Infuse®" were listed as approximately $900 million[20] for 2011. But it is important to note that 85% to 90%[21] of these "Infuse® sales" were not of the Infuse® device approved by the FDA. These sales were of the 1st Component of Infuse®; namely, the BMP/Sponge.

67. MSD expanded BMP/Sponge sales by paying large amounts of money to "Key Opinion Leader" ("KOL") spine surgeons around the country, many of whom then published articles, or appeared at special "dinners" or continuing education seminars advocating BMP/Sponge use in posterior approach surgeries, without the LT-CAGE™, while minimizing the risks or dangers of this experimental device, unapproved by the FDA.

68. The U.S. Senate in a special report found that MSD paid approximately $210 million to these KOLs who, in turn, improperly influenced and promoted the sale of the

[20] "Critique could put bigger drag on Infuse sales" (Oct. 25, 2012), available at http://www.startribune.com/business/175896771.html.

[21] *See* Emily Jane Woo, *Recombinant Human Bone Morphogenetic Protein 2: Adverse Events Reported to the Manufacture and User Facility Device Experience Database,"* The Spine Journal, 12 (10): 894-899, October 2012; *see also* John Carreyrou and Tom McGinity, *Medtronic Surgeons Held Back, Study Says*, Wall St. J. June, 29, 2011.

BMP/Sponge device.[22]

69. Medtronic also tied their sales representatives' compensation almost solely to their sales quotas for the 1st Component of Infuse® (the BMP/Sponge), but had no incentives or bonuses related to the sales of the 2nd component of Infuse® (the LT-CAGE™).

70. This compensation plan was purposeful and intended to increase sales of the BMP/Sponge for uses and in manners not approved by the Infuse® PMA, and contrary to PMA restrictions on Infuse®'s design and use.

71. Medtronic's reimbursement strategy with insurance carriers was also designed to, and did, promote the sale of its BMP/Sponge device into markets not approved for Infuse®.

72. The concerted efforts of the Medtronic Defendants and their KOLs were in violation of the FDCA and the MDA, for marketing, distribution and promotion of BMP/Sponge as a combination biologic/device, unapproved for such by the FDA.

73. The Medtronic Defendants' and their KOLs' promotion and marketing of the BMP/Sponge for use in spinal fusion surgeries created combination medical device different and distinct from Infuse®.

74. This BMP/Sponge device had not been subjected to adequate pre-clinical or clinical testing or FDA review and approval; thus, the BMP/Sponges implanted in Plaintiffs were experimental device, and were for that reason and others, unreasonably dangerous.

75. In addition to the BMP/Sponge, the Medtronic Defendants and their KOLs also promoted and marketed the BMP/Sponge with the P's Cages, and thus created a combination medical device different and distinct from Infuse®.

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[22] S. Comm. on Finance, 112th Cong., 2d Sess., *Staff Report on Medtronic's Influence on Infuse Clinical Studies* (Oct. 2012) ("Senate Report"). Attached hereto as Exhibit 13; also available at: http://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0CCYQFjAA&url=http%3A%2F%2Fo2.aolcdn.com%2Fhss%2Fstorage%2Fpatch%2F6fca5987e2c44fd011690ea8164f8cfa&ei=-ihAU87NK8jNsQTlq4CgAg&usg=AFQjCNFoz9RkjF-8Idi6HwIXyRRyLZzSqw.

76. The BMP/Sponges in combination with P's Cages had not been subjected to adequate pre-clinical or clinical testing or FDA review and approval; thus, the BMP/Sponges/P's Cages combination devices implanted in Plaintiffs were experimental devices, and were for that reason and others, unreasonably dangerous.

77. The Medtronic Defendants and their KOLs also promoted, marketed and/or knowingly distributed P's Cages for use with BMP, a biologic.

78. P's Cages were Class II medical devices and these devices had not been subjected to adequate pre-clinical or clinical testing or FDA review and approval as required by 21 CFR §888.3080; thus, P's Cages implanted in Plaintiffs were experimental devices, and were for that reason and others, unreasonably dangerous.

**D. MEDTRONIC AND ITS KOLS FALSELY PROMOTED AND MARKETED BMP.**

79. The Medtronic Defendants and their KOLs, working as co-conspirators, understood that spine surgeons learned of spinal procedures through various sources of information including: (a), medical literature; (b), medical conferences and seminars; (c), sales representatives from drug and device companies, like Medtronic; and, (d), consulting with peers in the spine surgery community.

80. Medtronic, with its KOLs, sales representatives and other agents, infiltrated each of the sources of information listed above.

81. Medtronic and its KOLs so systematically corrupted and tainted these sources of information that any spine surgeon or patient seeking the true safety and efficacy of BMP could base his/her opinion only on tainted and false information, either through explicit misrepresentations of fact or through the withholding of information when Medtronic, its KOLs, and its other agents had a duty to speak.

82. The falsehoods discussed above were material and were designed by the Medtronic Defendants to induce Plaintiffs to consent to the use of the BMP/Sponge with P's Cages.

83. Had the true risks and benefits not been falsely concealed from the Plaintiffs, and had the Plaintiffs known that the devices implanted in their surgery were essentially experimental devices, unapproved for marketing and use by the FDA, the Plaintiffs would not have consented to use these devices in the manner and in the combination in which these devices were used in Plaintiffs' surgeries.

84. Medtronic paid its KOLs large sums of money during relevant time periods both before and after Medtronic sold the BMP/Sponges and sold or recommended the use of P's Cages to Plaintiffs.

85. Both Medtronic and its KOLs knew and conspired to keep secret that its KOLs were simply highly paid salesmen of Medtronic products, and were not, as they appeared, objective scientists and investigators giving opinions regarding the safety and efficacy of Medtronic's BMP/Sponge, used either with its surgical fusion cages or similar cages produced by other companies designed for use in posterior approach surgeries.

86. In many cases, Medtronic sales representatives were present for the Plaintiffs' spinal fusion surgery.

87. At least one of the Plaintiffs was treated at a center that employed Medtronic's KOLs; yet, KOL surgeons failed to reveal their financial conflict of interest in using Medtronic products—whether BMP or P's cages—when both Medtronic and its KOLs had a duty to do speak and reveal these financial conflicts.

88. Regardless of whether Medtronic entered into an explicit fraudulent conspiracy with its KOLs, the Medtronic Defendants and their KOLs withheld the fact that Medtronic paid its KOLs huge sums of money based on the sales of Medtronic products. The Medtronic Defendants paid this money at the same time its KOLs made supposedly "unbiased," objective scientific statements regarding the risks and benefits of Medtronic's products, including the BMP/Sponge and P's Cages used with BMP.

89. As described in Paragraph 80 above, by withholding this financial conflict of interest, Medtronic and its KOLs corrupted the sources of information regarding the BMP/Sponge otherwise available to the medical community and/or to patients.

90. Medtronic and its KOLs had a legal and ethical duty to reveal this financial conflict of interest, and the true risks and benefits of the combination biologic/devices outlined above; yet, negligently and/or intentionally failed to do so.

**E. MEDTRONIC FALSELY MARKETED AND/OR PROMOTED P'S CAGES.**

91. In addition to the tapered LT-CAGE™ for anterior surgeries, the Medtronic Defendants also manufactured cages for use in posterior surgeries which were approved by the FDA as Class II medical devices.

92. These posterior cages were designed to be used with cadaver bone or harvested bone graft and were not designed or FDA approved to be used with a biologic, such as BMP.

93. In an effort to capture the PLIF market for both its BMP/Sponge and its Class II cages, Medtronic promoted combining the BMP/Sponge with its Class II surgical cages.

94. Medtronic, its agents and its KOLs negligently, recklessly and/or intentional represented that Class II cages (regardless of manufacturer) could safely and effectively be used with the biologic in its BMP/Sponge.

95. Neither of these devices (the BMP/Sponge and the Class II surgical cages) was approved by the FDA for this intended use.

96. Thus, the Medtronic Defendants promoted not only the use of its BMP/Sponge into markets unapproved for Infuse® but also falsely reassured physicians and patients that Class II surgical cages, such as the P's Cages, could safely and effectively be used with a biologic; namely BMP.

97. These Class II surgical cages, like the P's Cages, were completely untested for use with a biologic. Thus, surgeons ended up essentially guessing at proper doses of BMP with no clinical trial to determine how best to guide bone growth, either through the structure of the surgical cage or the amount of BMP used.

98. For instance, at the suggestion and encouragement of Medtronic's KOLs and its sales representatives, surgeons would cut-up the BMP/Sponge to make it fit in surgical cages not designed to be used with the BMP/Sponge device. Or, as explained below, Medtronic's sales representatives would suggest that surgeons roll the BMP/Sponge "like a taco" in order to fit it into various aspects of the spine, without a cage.

99. P's Cages varied, but the vast majority of P's Cages consisted of PEEK cages manufactured by Medtronic and were densely packed with BMP.[23]

100. In all but two cases, P's Cages had been approved for marketing by the FDA via a 510(k) procedure, which allowed for approval merely by showing that the cage was "substantially equivalent" to other products like it, already on the market.[24]

101. Although the Medtronic Defendants, their sales representatives and their KOLs

[23] *See*, Chart listing cage type and manufacturer, where available, for all Plaintiffs in the above-styled litigation pending in this Court, Exhibit 14.
[24] *See* chart listing 510(k) approval history for P's cages, Exhibit 14a.

were well-aware that P's Cages were being used for purposes for which they had not been tested or designed, Medtronic and its co-conspirators and agents encouraged to use of P's Cages with BMP, a biologic.

102. Under state law, Medtronic had a duty of due care in the design, testing, manufacturing, distribution and marketing of surgical cages it intended to be used with a biologic.

103. On June 12, 2007, the FDA promulgated 21 CFR §888.3080, requiring an "approved PMA" for surgical cages containing biologics, such as BMP.

104. Medtronic knew that the FDA promulgated 21 CFR §888.3080.

105. Despite having full knowledge of this regulation, Medtronic and its agents, including but not limited to its KOLs, continued to negligently and/or recklessly promote and distribute Class II cages, such as P's Cages relevant here, for use with a biologic, specifically the BMP/Sponge.

106. The LT-CAGE™[25] was approved for use as a Class III device, which is the most rigorous form of approval possible by the FDA.

107. The LT-CAGE™ is made of titanium and was specially designed to be implanted through the front of the spinal column.

108. The vast majority of P's Cages were made of polyetheretherketone (PEEK) and designed to be used only in a posterior surgical approach.

109. All but two of P's cages were approved via the 510(k) process and were not approved via the FDA's most stringent approval process for Class III devices via a PMA

[25] *See,* Zdeblick, TA, Burkus, JK, "LT-CAGE™, Lumbar Tapered Fusion Device Surgical Technique," attached hereto as Exhibit 15, at page 17.

Process.[26]

110. The Medtronic Defendants, their sales representatives, their KOLs (as well as other agents) advised Plaintiffs and/or Plaintiffs' surgeons that use of such Class II PEEK cages, including P's Cages, was safe and effective and failed to inform Plaintiffs that P's Cages were experimental device, unfit and untested for use with a biologic, like BMP.

111. Medtronic Defendants, through their sales representatives, witnessed multiple surgeries involving the misuse of these Class II devices; yet, Medtronic took no measure to warn against the use of these devices.

112. Medtronic knew that these Class II cages should be re-designed and tested for safe and effective use with a biologic prior to implantation in a posterior approach spine surgery.

113. Despite having this knowledge, Medtronic continued to promote the use of the BMP/Sponge in combination with Class II cages. In this way, Medtronic created, marketed, and promoted an experimental device, without FDA approval and without adequate testing, that was unreasonably dangerous.

114. The BMP/Sponge was implanted using without the LT-CAGE™.[27]

115. P's Cages, in contrast to the LT-CAGE™ approved as part of the Infuse® device, are differently designed, are for different surgical approaches, and are made of different materials. Different regulatory approvals from the FDA apply to the use of the LT-CAGE™, versus P's Cages.

116. The Medtronic Defendants promoted and marketed to Plaintiffs P's cages, which were distinct medical devices untested for the use recommended by these Defendants.

[26] *See* 510(k) approval history, Exhibit 14a.
[27] In some cases, no cage was used at all. *See, e.g.*, Exhibit 14, Chart listing cages used in Plaintiffs' procedure.

117. Such uses were never reviewed or approved by the FDA and such promotion and marketing was contrary to FDA regulations, the FDCA and the MDA.

118. Medtronic's highly paid KOLs, on its behalf, promoted these types of devices, teaching surgeons to use them.

119. Such uses were never reviewed or approved by the FDA and such promotion and marketing was contrary to FDA regulations, the FDCA and the MDA.

120. P's Cages were not designed or tested to contain a biologic, like BMP.

121. P's Cages were designed to be used in posterior approach surgeries, not ALIF surgeries as required by the FDA in its approval of Infuse®.

122. Thus, P's Cages allowed an uncontrolled, untested and unpredictable rate of absorption of BMP which allowed for the overgrowth of bone.

123. Also, unlike the LT-CAGE™, P's Cages did not contain or direct the growth of bone to avoid injury to the spinal cord or nerve roots.

**F. DAMAGES AND INJURIES CAUSED THE PLAINTIFFS.**

124. Following their surgeries, the Plaintiffs did not improve, but continued to suffer additional, new and/or in some cases worse pain, suffering, symptoms and disability.

125. An unacceptable incidence rate of adverse events results when the BMP/Sponge is used in surgeries other than ALIF, and without the LT-CAGE™, which was designed and tested to contain the BMP/Sponge.

126. The Plaintiffs suffered these injuries because BMP, when used in any fashion other than as approved in the PMA for Infuse®, is an untested experimental surgical product, and for that reason is unreasonably dangerous.

127. BMP, when used in the fashion of Plaintiffs' surgeries, caused excess bone growth and impingement on the nerve roots and the spinal cord which spinal fusion surgery using autographs was designed to and was proven to relieve.

128. As more specifically explained below, Medtronic's unreasonably dangerous products sold to Plaintiffs, and the negligent and/or intentional statements or omissions made by the Medtronic Defendants and its KOLs, were substantial factors in causing Plaintiffs' injuries.

**G. INFUSE® PMA IS COMPLETELY INAPPLICABLE.**

129. The Medtronic Defendants never applied to the FDA for approval for the medical devices it created for implantation into Plaintiffs.

130. The Medtronic Defendants never sought FDA-approval of the use of the BMP/Sponge alone or in combination with P's Cages.

131. The Medtronic Defendants never formulated any directions and warnings for P's Cages and/or the BMP/Sponge, as they were used in Plaintiffs' fusion surgeries.

132. There were no FDA-imposed requirements specific to these devices implanted into Plaintiffs because the Medtronic Defendants never sought FDA approval for these medical devices prior to their marketing, sale, and eventual implantation into Plaintiffs.

133. As used in Plaintiffs, the use, application and safety and effectiveness of the BMP/Sponge and P's Cages were wholly outside of the FDA's regulatory framework and the PMA for Medtronic's Infuse®.

**H. THE MEDTRONIC DEFENDANTS VIOLATED FEDERAL LAW, PARALLEL TO PLAINTIFFS' STATE LAW CLAIMS.**

134. It was and is illegal for the Medtronic Defendants or any of their sales representatives to market and distribute the biologic/devices outlined above for use in Plaintiffs' fusion surgeries.

135. The Medtronic Defendants were aware that their promotion, marketing and sales of the BMP/Sponge would result in it becoming "misbranded" in violation of 21 U.S.C. § 352(f).

136. The Medtronic Defendants were aware that their promotion of P's Cages (which these Defendants manufactured) for use with a biologic, like BMP, would result in P's Cages becoming "misbranded" in violation of 21 U.S.C. § 352(f).

137. The Medtronic Defendants were aware that distribution by them of these "misbranded" medical devices is and was prohibited pursuant to 21 U.S.C. §§ 331(a), (k) and 21 U.S.C. § 352(f).

138. In doing the acts alleged herein, the Medtronic Defendants: (a) did not act reasonably with regard to the foreseeable harm to patients, including Plaintiffs; (b) did not act as a responsible manufacturer of Class II or Class III medical devices; (c) acted unlawfully, in violation of the Infuse® PMA (to the extent, if any applicable); (d) acted unlawfully, in violation of the FDA regulations; and/or (e) violated state common law duties, all of which parallel and are ***not*** in addition to or different from FDA and federal requirements.

139. Plaintiffs bring their causes of action solely under state law for full redress for the injuries and damages they have suffered and have proximately incurred and will incur as a result. Plaintiffs here do not seek any remedy under federal law, or assert any cause of action under such laws. Product liability claims asserted herein allege traditional state law causes of action embedded within a horrific and cynical scheme of promoting unapproved medical products and/or "off/label" promotion. The facts supporting these common law theories of recovery are parallel to and consistent with repeated violations, by the Medtronic Defendants, of the Medical Device Amendments of 1976 ("MDA") and FDA regulations. Facts relating to this scheme of off-label promotion are more specifically alleged below.

## IV. FACTS

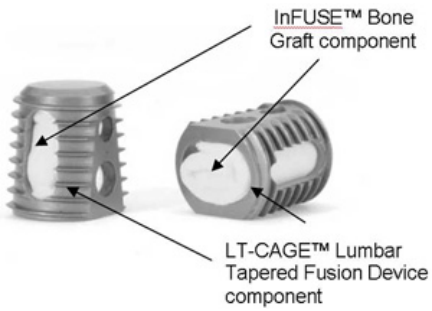
### A. THE INFUSE® BONE GRAFT DEVICE.

140. The Medtronic Defendants manufactured, designed, marketed, promoted, and sold Infuse® for use in lumbar spine fusion surgeries.

141. Infuse® contains a bioengineered bone-protein known as recombinant bone morphogenetic protein-2 ("rhBMP-2"), and it is used as an alternative to bone grafting, which involves the transplantation of a piece of bone from the patient's own hip (or bone from a cadaver) to the spine to promote bone growth. The purported goal of Infuse® is to achieve the ultimate outcome of bone transplantation by stimulating bone growth with the use of rhBMP-2 without producing the possible adverse side effects of a bone grafting procedure, which can be pain at the donor site.

142. As an alternative to traditional grafting/transplantation procedures, Infuse® uses a protein known as rhBMP-2 (extracted from genetically-engineered cells which originate from the ovaries of Chinese Hamsters) to facilitate the fusion of vertebrae.

143. The Infuse® "device" is a "system" that combines two components consisting of three parts: (1) the bone protein, rhBMP-2, soaked into an absorbable collagen sponge (ACS); and, (2) a metallic spinal fusion cage, called an "LT-CAGE™". The collagen "sponge" or "scaffolding" is manufactured from bovine collagen and used as a carrier for the protein, placed inside the fusion cage.



144. The LT-CAGE™ allegedly maintains the spacing between vertebrae and temporarily stabilizes the diseased region of the spine, while the Infuse® bone graft component is used to form bone, with the goal of permanent stabilization (fusion) of the spine.

145. During surgery, rhBMP-2 is soaked onto and binds with the absorbable collagen sponge that is designed to resorb, or disappear, over time. As the sponge dissolves, the rhBMP-2 is designed to stimulate the cells to produce new bone.

### B. BACKGROUND ON BONE MORPHOGENETIC PROTEIN IN THE INFUSE® BONE GRAFT.

146. Surgeons have for decades employed spinal fusion – a surgical technique in which one or more of the vertebrae of the spine are united together ("fused") so that motion no longer occurs between them – to treat a number of spinal conditions and deformities.

147. For years, autologous bone graft has been considered the "gold standard" in spinal fusion surgery. In an autologous bone graft, or "autograft," the surgeon procures bone graft material from another part of the patient's body, typically from the patient's pelvis or iliac crest, and implants the bone graft in the site where fusion is desired.

148. Consequently, studies revealing the ability for biologically manufactured protein to generate bone growth in laboratory animals represented a potential to provide a third surgical option to traditional bone graft procedures. The theory was that, if fusion could be accomplished through the use of biologically manufactured proteins, patients could forego the harvest surgery required in an autograft, but could still benefit from the superior fusion rates associated with autograft procedures.

### C. BACKGROUND INFORMATION ON THE CORPORATE OWNERSHIP OF INFUSE®

149. Genetics Institute, Inc. identified, isolated, purified and cloned the bone morphogenetic protein known as BMP-2.

150. Sofamor Danek Group, Inc., a Memphis, Tennessee based spinal device maker ("Sofamor Danek"), acquired the exclusive rights to the recombinant human bone morphogenetic rhBMP-2 for spinal applications in the United States from Genetics Institute in February 1995.

151. Under the agreement, Sofamor Danek acquired the exclusive right in North America to develop and commercialize these products for spinal applications. Sofamor Danek paid Genetics Institute, Inc. $12.5 million in license fees in 1995 and was obligated to pay up to $37.5 million starting in 1996 through 1998. Genetics Institute, Inc. retained the exclusive right to manufacture rhBMP-2 for supply to Sofamor Danek. Genetics Institute, Inc. and Sofamor Danek agreed to equally share revenues.[28]

152. Wyeth Pharmaceuticals, shortly after this agreement, acquired Genetic Institute, Inc. and the rights to rhBMP-2 in 1996.[29]

153. In October 1996, Sofamor Danek filed an application for an Investigational Device Exemption ("IDE") with the FDA to conduct a pilot study on the effects of rhBMP-2 in humans, marking the first step to obtaining approval to commercially market rhBMP-2.[30]

154. In January 1999, Medtronic purchased Sofamor Danek for $3.6 billion.[31]

155. In 2009, Pfizer acquired Wyeth for $68 billion.[32]

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[28] Genetics Institute and Sofamor Danek to Collaborate on Spinal Indication for rhBMP-2, (Feb 16, 1995), attached hereto as Exhibit 16, also *available at:* http://www.thefreelibrary.com/GENETICS+INSTITUTE+AND+SOFAMOR+DANEK+TO+COLLABORATE+ON+SPINAL...-a016518853

[29] Wyeth Quietly Turns Itself Into A Biotech Power (Nov 23, 2007), attached hereto as Exhibit 17, also *available at* http://www.blnz.com/news/2008/02/19/Wyeth_Quietly_Turns_Itself_Into_7301.html.

[30] Bone Morphogenic Proteins: Applications in Spinal Surgery (Sep 2005), *available at* http://www.ncbi.nlm.nih.gov/CBH/articles/CBH2504139/ (also attached hereto as Exhibit 18).

[31] Medtronic to Buy Maker of Spine Implants for $3.6 Billion, *LA Times*, (Nov 3, 1998), *available at* http://articles.latimes.com/1998/nov/03/business/fi-38827 (also attached hereto as Exhibit 19).

### D. REGULATORY FRAMEWORK

156. To understand the full scope of the allegations contained in this Complaint, a brief general background regarding the applicable FDCA provisions is warranted, as well as an application of those laws to the present case.[33]

157. The United States Food and Drug Administration ("FDA") is the federal agency of the United States of America that is charged with safeguarding the health and safety of the public by enforcing the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 301, *et seq*. (2012) (the "FDCA").[34]

158. The FDCA was passed in 1933 to protect patients. Congress realized that there were drug manufacturers selling drugs that were neither effective nor safe. Congress felt that regulations were necessary to protect patients by making the drug manufacturers go through an approval process before they would be legally permitted to promote their drugs for specific indications.

159. In 1976, there were the Dalkon Shield contraceptive tragedies where numerous patients were harmed by that medical device. Congress responded by enacting the Medical Device Amendments of 1976 ("MDA") to extend the coverage of the FDCA to medical devices. The MDA was passed to protect patients with the idea that medical devices should be subjected to a rigorous approval process *for specific indications* and before medical device manufacturers

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[32] *See* Aaron Smith, *Pfizer to buy Wyeth for $68 billion*, CNNMoney.com (Jan. 30, 2009) *available at* http://money.cnn.com/2009/01/26/news/companies/pfizer_wyeth/ (also attached hereto as Exhibit 20).

[33] Plaintiffs are not seeking to enforce these provisions in this action. Likewise, Plaintiffs are not suing merely because the Medtronic Defendants' conduct violates these provisions. Rather Plaintiffs are alleging that Medtronic's conduct that violates these federal regulations, as well as the PMA obtained for Infuse®, also violates parallel state laws. Plaintiffs make these allegations anticipating that the foremost (if not the only defense) the Medtronic Defendants will have to Plaintiffs' state law violations will be their affirmative defense of preemption.

[34] The ultimate responsibility for the safety of a medical device, of course, rests with the Manufacturer.

are allowed to market them. Therefore, the FDA has authority over drugs and medical devices under the FDCA and the MDA.

160. The MDA established three regulatory classes for medical devices. The three classes are based on the degree of control necessary to assure that the various types of devices are safe and effective according to user risk. Class I medical devices pose the least risk, whereas Class III medical devices pose the greatest risk to the users.[35]

161. Class I devices are subject to "general controls" such as labeling requirements.[36] Class II devices are subject not only to "general controls," but also to "special controls" such as "performance standards, postmarket surveillance, [and] patient registries."[37] If a device cannot be determined to provide a reasonable assurance of safety and effectiveness under Class I or II controls and is either marketed as a life supporting device or may cause an unreasonable risk of illness or injury, then it rises to the level of a Class III medical device.[38]

162. Class III medical devices are the most regulated. The MDA defines a Class III medical device as one that supports or sustains human life or is of substantial importance in preventing impairment of human health or presents a potential, unreasonable risk of illness or injury.[39]

163. Class III medical devices pose the greatest risk of death or complications and include most implantable surgical devices such as cardiac pacemakers, coronary artery stents, and several types of implantable orthopedic devices for spine and hip surgery. Medtronic's Infuse® is a Class III medical device because it combines a surgical fusion cage designed to

[35] 21 U.S.C. § 360c(a)(1) (2012).
[36] 21 U.S.C. § 360c(a)(1)(A) (2012).
[37] 21 U.S.C. § 360c(a)(1)(B) (2012).
[38] 21 U.S.C. § 360c(a)(1)(C) (2012).
[39] *Id.*

contain a biologic, like BMP.[40]

164. P's Cages are Class II medical devices, unapproved for use with a biologic. *If* the manufacturer intends to use such cages with a biologic (as Medtronic did here), the manufacturer at that point is required to obtain PMA approval for use of the device with a biologic.[41]

165. FDA regulations prohibit biologics, such as the rhBMP2 in Infuse®, to be used in a surgical cage that has not been vetted for that use by the FDA through its Pre-market Approval ("PMA") process as a Class III device, explained below.[42]

**1. Premarket Approval ("PMA") Process For Class III Medical Devices.**

166. The MDA imposes detailed federal oversight on the introduction of new medical devices onto the market. The level of federal oversight varies depending on the risks the devices present. Class III medical devices are given the greatest oversight in the pre-market approval process ("PMA") by the FDA.[43]

167. Before a company can market a Class III medical device, the company is required to submit a premarket application to the FDA supported by data that provides the FDA with a reasonable assurance that the medical device is safe and effective for its *intended use*.[44] In order to show safety and effectiveness, the applicant is required to submit evidence to the FDA, typically in the form of clinical trial results.

168. Without a premarket application, there is insufficient information about Class III medical devices so that performance standards (Class II) or general controls (Class I) cannot provide reasonable assurance that the medical device is safe and effective for its specific intended use.

[40] *See* "Guidance for Industry and FDA, Class II Special Controls Guidance Document: Intervertebral Body Fusion Device," attached hereto as Exhibit 10.
[41] *Id.*
[42] 21 CFR § 888.3080.
[43] 21 U.S.C. § 360c(a)(1)(C).
[44] 21 U.S.C. §§§ 360e(a)(2), 360e(d)(1)(B)(iii)II, 360e(d)(2)(A).

169. Under Section 515 of the FDCA, all medical devices placed into Class III are subject to premarket approval requirements. Premarket approval by FDA is the required process of scientific review in order to provide reasonable assuredness of the safety and effectiveness of Class III devices for their *intended uses*.[45]

170. The applicant must provide, among other things: 1) "a detailed description of the proposed conditions of use of the device,"[46] 2) a sample label, which must include the *intended uses* or conditions of use,[47] and 3) "full reports of all information, published or known to or which should reasonably be known to the applicant, concerning investigations which have been made to show whether or not such device is safe and effective."[48]

171. To determine if a medical device is safe and effective, the FDA reviews the scientific evidence regarding the medical device submitted by the applicant, including "evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device *under its conditions of use*."[49]

172. "There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its *intended uses* and conditions of use, when accompanied by *adequate directions and warnings against unsafe use*, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of

[45] 21 U.S.C. § 360e (emphasis added).
[46] 21 U.S.C. § 360c(a)(3)(D)(i).
[47] 21 U.S.C. § 360e(c)(1)(F) (2012); see also 21 U.S.C. § 360c (2)(B).
[48] 21 U.S.C. § 360e(c)(1)(A).
[49] 21 C.F.R. § 860.7(c)(2) (emphasis added).

illness or injury associated with the use of the device for its intended uses and conditions of use."[50]

173. "[T]he safety and effectiveness of a device are to be determined (A) with respect to the persons for whose use the device is represented or intended, (B) with respect to *the conditions of use* prescribed, recommended, or suggested in the labeling of the device, and (C) weighing any probable benefit to health from the use of the device against any probable risk of injury or illness form such use."[51]

174. After the FDA finishes review of the premarket application, it then denies, approves, or approves with conditions on distribution, marketing, or sale.[52]

175. "In making the determination whether to approve or deny the application, the Secretary shall rely on the conditions of use included in the proposed labeling as the basis for determining whether or not there is a reasonable assurance of safety and effectiveness."[53]

176. After the FDA approves a Class III medical device through the premarket application process, the FDA essentially grants the applicant permission to market and sell a particular medical device for its *specific approved use* (i.e. its "*intended use*").

177. "*A device may not be manufactured, packaged, stored, distributed, or advertised in a manner that is inconsistent with any conditions to approval specified in the PMA approval order for the device*."[54]

**2. PMA Applications Are Limited by the Claimed "*Intended Use.*"**

178. The PMA is based on the manufacturer disclosing all of the pertinent information about the medical device for the FDA to review. One of the most significant parts of the

[50] 21 C.F.R. § 860.7(d)(1) (emphasis added).
[51] 21 U.S.C. § 360c(a)(2) (emphasis added).
[52] 21 U.S.C. § 360e(d); 21 C.F.R. § 814.82.
[53] 21 U.S.C. § 360e(d)(1)(A).
[54] 21 C.F.R. § 814.80 (emphasis added).

premarket application is the medical device's claimed "*intended uses*" as these are the only uses that are evaluated by the FDA in their premarket approval process for efficacy and safety.[55] The Code of Federal Regulations (C.F.R.), Title 21, Chapter I, Subchapter H—Medical Devices, § 801.4 (2012) (Meaning of intended uses.), defines "intended use" in terms of "objective intent" of the manufacturer in a medical device approval setting:

> The words intended uses or words of similar import in 801.5, 801.119, and 801.122 refer to the objective intent of the persons legally responsible for the labeling of devices. The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article. **This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives.** It may be shown by the circumstances that the article is, **with the knowledge** of such persons or their representatives, **offered and used for a purpose for which it is neither labeled nor advertised**. The intended uses of an article may change after it has been introduced into interstate commerce by its manufacturer…But **if a manufacturer knows, or has knowledge of facts that would give him notice that a device introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a device which accords with such other uses** to which the article is to be put.[56]

179. The FDCA requires Class III medical devices to be demonstrated to be safe and effective for each *intended use*.[57]

180. The FDA ensures that medical devices intended for use in humans are demonstrated by the manufacturer to be safe and effective for each of their *intended uses* and that the labeling of such medical devices contain true and accurate information concerning their intended use.[58]

181. The FDA determines what is on label on the basis of a product's "intended

[55] 21 U.S.C.§ 360e(c)(2)(A)(iv); *see* also 21 U.S.C. § 360c(a)(2)(A-B).
[56] 21 C.F.R. § 801.4 ("Meaning of 'Intended Uses'" under the "General Labeling Provisions" for the "Labeling" section.) (Emphasis added).
[57] *See* 21 U.S.C. § 360c(2)(B).
[58] *Id.*

use."[59]

### 3. The PMA Approval Process Includes the Device and Its Labeling.

182. Not only is the medical device itself part of the PMA process, but the labeling and packaging that comes with it is as well. Each premarket submission must also include all proposed "labeling" for the medical device and *its intended use*.[60]

183. The FDCA requires that a submission for approval of a device include proposed labeling for the proposed *intended uses* of the medical device that includes, among other things, the conditions for therapeutic use.[61]

184. In order to be approved by the FDA, an applicant for premarket approval of a Class III medical device must demonstrate its safety and effectiveness for "the persons for whose use the device is represented or intended" and "with respect to the conditions of use prescribed, recommended, or suggested in the label…"[62]

185. The FDA performs a risk-benefit assessment of the medical device and then determines the adequacy of the manufacturer's proposed label. When the FDA approves a premarket application, the FDA finds that based on the information supplied by the manufacturer, a device is safe and effective under the specific and limited conditions of use included on the label and that the label is not false or misleading.[63]

186. A manufacturer is required to give adequate directions for the use of a medical device such that a "layman can use a device safely and for the purposes for which it is intended"[64], and conform to section 801.15 requirements governing the appearance of the label.[65]

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[59] *Id.*
[60] *Id.*
[61] *Id.*
[62] 21 U.S.C. § 360c(a)(2)(A)-(B).
[63] 21 U.S.C. § 360e(d)(1)(A), (d)(2) (A-B-C-D).
[64] 21 C.F.R. § 801.5.

> **Adequate directions for use means directions under which the layman can use a device safely and for the purposes for which it is intended.** Section 801.4 defines intended use. Directions for use may be inadequate because, among other reasons, of omission, in whole or in part, or incorrect specification of:
>
> (a) **Statements of all conditions, purposes, or uses for which such device is** intended, including conditions, purposes, or uses for which it is prescribed, recommended, or suggested in its oral, written, printed, or graphic advertising, and conditions, purposes, or uses for which the device is commonly used…
>
> (b) Quantity of dose, including usual quantities for each of the uses for which it is intended and usual quantities for persons of different ages and different physical conditions…
>
> (f) Route or method of administration or application.[66]

187. "Labeling" encompasses all written, printed or graphic material accompanying the drug or device[67], and therefore broadly encompasses nearly every form of promotional activity, including not only "package inserts" but also advertising.[68]

188. Labeling includes the intended purpose as well as any advertised or promoted purposes.

> Labeling on or within the package from which the device is to be dispensed bears **information for use, including indications**, effects, routes, methods, and frequency and duration of administration, and any relevant hazards, contraindications, side effects, and precautions under which practitioners licensed by law to administer the device can use the device safely and **for the purpose for which it is intended, including all purposes for which it is advertised or represented**: Provided, however, that such information may be omitted from the dispensing package if, but only if, the article is a device for which directions, hazards, warnings, and other information are commonly known to practitioners licensed by law to use the device. Upon written request, stating reasonable grounds therefor, the Commissioner will offer an opinion on a proposal to omit such information from the dispensing package under this proviso."[69]

189. "Most, if not all, labeling is advertising. The term "labeling" is defined in the

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[65] 21 C.F.R. § 801.15.
[66] 21 C.F.R. § 801.5.
[67] *Id*. 65 Fed. Reg. 14286 (March 16, 2000).
[68] 21 C.F.R. § 801.109(c).
[69] 21 C.F.R. §801.109(c). (Emphasis added.)

FDCA as including all printed matter accompanying any article. Congress did not, and we cannot, exclude from the definition printed matter which constitutes advertising."[70]

**4. FDA Regulations and PMA Process Prohibit "Off-Label" Promotion.**

190. When the FDA approves a medical device, the agency approves the device for the specific intended use set out in the product's approved labeling. A use approved by the FDA is usually referred to as an "approved", "labeled" or "intended use". A use that does not appear in the labeling is not approved as safe and effective as it never went through the FDA's PMA review. It is known as an "unapproved," "off-label," or "new use." For the sake of consistency, in this complaint, Plaintiffs refer to such unapproved uses as "off-label".

191. A medical device manufacturer is not permitted to promote and/or market a new medical device submitted to the FDA under the premarket approval process until it has an approval for its intended use, including approval for the proposed labeling. Moreover, if approved, the medical device manufacturer is permitted to promote the medical device only for the medical conditions or *indicated uses* specified in the approved labeling. Therefore, a medical device manufacturer is not permitted to promote a medical device in an "off-label" manner, since the FDA did not approve the medical device for that medical condition or use.

192. A central feature of the FDCA is that it prohibits medical device companies from promoting their devices for "off-label" uses.[71]

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[70] *U.S. v. Research Labs.*, 126 F.2d 42, 45 (9th Cir. 1942).

[71] Congress created a very limited "safe harbor" for certain "off-label" promotion between 1997 and 2006. The "safe harbor" allowed manufacturers to provide copies of peer reviewed scientific articles to physicians. See 21 U.S.C. §§ 360aaa, 360aaa-1 (2012) (these regulations had a sunset clause of September 30, 2006 and were never renewed, see 21 C.F.R. §§ 99.101 (2012) (current FDA regulations on this issue)). As further discussed herein, Plaintiffs, however, allege that Medtronic's "off-label" promotional efforts far exceeded these "safe harbor" activities (i.e. redistribution of peer reviewed articles) and included other impermissible acts, including but not limited to, using paid consultants, key opinion leaders, seminars, presentations, in-house corporate paid doctors operating phone banks to instruct outside surgeons over the phone when they call Medtronic headquarters on how to perform "off label" procedures, as well as drafting, editing and ghostwriting the so-called "peer reviewed articles"

> The Federal Food, Drug, and Cosmetic Act of 1938 (FDCA), as amended, **generally prohibits the manufacturer of a new drug or medical device from distributing a product in interstate commerce for any intended commerce for any intended use that FDA has not approved as safe and effective.** The intended use or uses of a drug or device may be set forth in, among other things, its label or "labeling," which includes written, printed, or graphic matter affixed to or "accompanying" the product. See 21 U.S.C. 321(m); 21 C.F.R. 202.1(1)(2); see also 21 C.F.R. 201.128, 801.4. The intended use or uses of a drug or device may also be determined from advertisements, promotional material, oral statements by the product's manufacturer or its representatives, and any other relevant source. *Action on Smoking and Health v. Harris*, 655 F.2d 236, 239 (D.C. Cir. 1980); see also 21 C.F.R. 201.128 and 801.4.
>
> **When FDA approves a drug or medical device, the agency approves the product for each use set out in the product's approved labeling.** A use that FDA approves is thus sometimes referred to as an "approved" or "labeled" use. A use that does not appear in the labeling is not approved as safe and effective by FDA and is known as an "unapproved" or "off-label" use.
>
> A central feature of the FDCA is that it generally prohibits interstate commerce in new drugs and devices for "new uses"… **Similarly, a medical device that is distributed for a "new use" is "adulterated," see 21 U.S.C. 351 (f), and "misbranded," see 21 U.S.C. 352(f). An adulterated or misbranded product is prohibited from distribution in interstate commerce (21 U.S.C. 331(a), (k))**…[72]

193. "[O]ne of the [FDCA's] core objectives is to ensure that any product regulated by the FDA is 'safe' and 'effective' for its intended use."[73]

194. A medical device that is promoted for non-intended "off-label" uses is deemed "misbranded" in violation of 21 U.S.C. § 352(f) (2012) (misbranding).

195. Under the FDCA and its accompanying regulations, a medical device manufacturer must include all intended uses in the label; otherwise the medical device is misbranded.[74]

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while paying the listed "authors" (who are acting as agents for the company) millions of dollars without disclosing these efforts or payments within the contents of the articles or anywhere publically, all to actively and consciously over promote the "off-label" uses of Infuse®.

[72] 65 Fed. Reg. § 14286 (March 16, 2000). (Emphasis added.)

[73] *United States v Caronia*, 703 F.3d 149, 166 (2nd Cir. 2012) quoting *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 133, (2000).

196. A product is "misbranded" when the directions and indications for the unapproved uses that the manufacturer "intends" the product to be used for have not been included on the label.[75]

197. The FDCA's accompanying regulations require that medical devices sold by manufacturers have adequate directions for use[76], and failure to have adequate instructions for use is considered "misbranding,"[77] which is prohibited.[78]

198. The FDCA requires medical device manufacturers to disclose all material facts in advertising and labeling[79], and false or misleading labeling is considered "misbranded"[80], which is prohibited.[81]

199. The distribution of a "misbranded" medical device is prohibited pursuant to 21 U.S.C. § 331(a), (k) (2012) and 21 U.S.C. § 352(f) (2012).

200. The FDCA provides that a medical device is misbranded if, among other things, the labeling did not contain adequate directions for use.[82] Adequate directions for use could not be written for medical indications or uses for which the medical device has not been approved, and accordingly, directions for "off-label" use cannot be included in the approved labeling.

201. "Similarly, a medical device that is distributed for a 'new use' is 'adulterated,' see 21 U.S.C. 351(f), and 'misbranded,' see 21 U.S.C. § 352(f). An adulterated or misbranded product is prohibited from distribution in interstate commerce (21 U.S.C. § 331(a), (k))…"[83]

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[74] 21 C.F.R. § 801.4.
[75] 21 C.F.R. § 801.4.
[76] 21 C.F.R. § 801.5.
[77] 21 U.S.C. § 352 (f).
[78] 21 U.S.C. § 331 (b).
[79] 21 U.S.C. § 321 (n).
[80] 21 U.S.C. § 352 (a),(q)(1).
[81] 21 U.S.C. § 331 (b).
[82] 21 U.S.C. § 352 (f)(1) (2012); *See also* 21 C.F.R. § 801.5.
[83] Fed. Reg. § 14286 (Mar. 16, 2000).

The reason a medical device that is distributed for an unapproved new use is considered 'misbranded' is that the device fails to include adequate directions and warnings.

202. "Off-label" use of a medical device is a use that was not approved by the FDA, including different applications or surgical approaches, different dosages, different patient populations, or different conditions from those stated in the label.

203. The FDA prohibits medical device manufacturers from promoting any "off-label" uses through advertisement, recommendations, or suggestions.

204. A manufacturer is prohibited from promoting a use of the product that is not the specified use in the PMA or the label.[84]

205. A manufacturer who wishes to modify the labeling, packaging, design, or indications for use of its device has to comply with a supplemental PMA process.[85]

206. The FDA strictly regulates manufacturers based on the intended use of the device, and manufacturers cannot deviate from those specifications without permission. If a manufacturer wants to change the intended use for a device, it must follow the FDA's established procedure.[86]

207. Federal law requires a manufacturer to ensure that any warranty statements it voluntary makes are truthful, accurate, not misleading, and consistent with applicable federal and state law.[87]

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[84] 21 U.S.C. § 331(a) (effective 2013); see also 21 C.F.R. § 814.80 (providing that a "device may not be… advertised in a manner that is inconsistent with any conditions to approval specified in the PMA approval order to the device.")

[85] 21 C.F.R. § 814.39(a).

[86] *See* 21 C.F.R. § 814.39(a) (specifying how a manufacturer can add new indications for use through the supplemental PMA process); 21 U.S.C. § 360e(d)(6).

[87] 21 U.S.C. § 331(b) (effective 2013). It should be noted that the FDA approval letter for Infuse® specifically states that the FDA "…does not evaluate information related to contract liability warranties, however you should be aware that any such warranty statements must be truthful, accurate, and not misleading, and must be consistent with applicable Federal and State laws." *See* Exhibit 1.

208. Under the FDCA and its accompanying regulations, a medical device manufacturer must include all intended uses in the label otherwise the device is misbranded.[88]

209. Under the FDCA, medical device manufacturers are prohibited from introducing the adulteration or misbranding of any medical device into interstate commerce.[89]

210. A Class III device that fails to meet and/or comply with the requirements of the PMA is considered to be adulterated under Section 501(f) of the FDCA and cannot be marketed. A device may also be adulterated or misbranded because it lacks requisite FDA clearance or approval.[90] Furthermore, "[l]isting of unapproved uses in the... advertising... results in an adulterated medical device."[91] Marketing the device for an unapproved intended use thus makes the device both misbranded and adulterated.

211. The FDCA prohibits the introduction into interstate commerce of any medical device that is misbranded[92], and also prohibits the alteration of any part of the labeling, advertising, or promotional material for a medical device while the device is held for sale after shipment in interstate commerce that results in the device being misbranded.[93]

212. A medical device manufacturer may not tell the FDA that its device should or will be used only in certain procedures, and then actively encourage physicians to use the device in other procedures. By promoting and/or advertising the medical device to physicians for a new unapproved use the medical device manufacturer has shown that the intended use of the device has changed. Off-label promotion violates federal law, the PMA and may carry criminal

[88] 21 C.F.R. § 801.4.
[89] 21 U.S.C. § 331(b) (effective 2013).
[90] FDCA §§ 501(f), 502(o), 21 U.S.C. §§ 351(f), 352(o).
[91] 59 Fed. Reg. 59821 (Nov. 18, 1994).
[92] 21 U.S.C. § 331(a) (effective 2013).
[93] 21 U.S.C. § 331(k) (effective 2013).

penalties, as well as violating state common law.[94]

**5. FDA Regulations Prohibit Distribution for "Off-Label" Uses.**

213. The FDA "generally prohibits the manufacturer... from distributing a product... for any intended use that the FDA has not approved as safe and effective...."[95]

214. "If a manufacturer knows, or has knowledge of facts that would give him notice that a device… is to be used for conditions, purposes, or uses other than the ones for which he offers it, the manufacturer is required to provide adequate labeling for such other uses."[96]

215. FDA regulations prohibit a manufacturer from "express[ing]" an "intent" or merely "know[ing]" or having "notice" that its product "is to be used" "off-label".[97]

216. Thus, a manufacturer that knows a device is being used for "off-label" uses is required to notify the FDA and obtain approval for labeling modifications consistent with the alternate use. Failure to do so renders the device adulterated and misbranded.

217. The FDCA prohibits the introduction, or delivery for introduction, into interstate commerce of any device that is adulterated or misbranded.[98]

218. FDA regulations also prohibit a manufacturer from "express[ing]" an "intent" or merely "know[ing]" or having "notice" that its product "is to be used" "off-label".[99] Any

[94] *See* 21 U.S.C. § 333(a). This conduct also violates State parallel common laws. The Second Circuit held that "off-label promotion that is false or misleading is not entitled to First Amendment protection." *United States v. Caronia*, 703 F.3d 149, 160-69 (2d Cir. 2012). Further, the Ninth Circuit has assumed that "off-label" promotion violates federal law. *Carson v. Depuy Spine, Inc.*, 365 Fed. App'x 812, 815 (9th Cir. 2010).
[95] 65 Fed. Reg. § 14286 (Mar. 16, 2000).
[96] 21 C.F.R. § 801.4. An example of direct knowledge would be when the manufacturer has a sales representative in the operating room. An example of notice would be when the manufacturer has a majority of sales for non-approved off-label uses.
[97] 21 C.F.R. §§ 201.100, 201.128; *see* 21 U.S.C. § 352(f)(1).
[98] 21 U.S.C. § 331(b) (2012).
[99] *See* 21 C.F.R. §§ 201.100, 201.128; *see also* 21 U.S.C. § 352(f)(1). The Medtronic Defendants routinely had Corporate Sales Representatives directly in the operating room during "off-label" surgeries. As further discussed herein, Medtronic's sales of Infuse® were over 85-90% "off-label". This staggering high statistic is sufficient evidence to not only put the Medtronic Defendants on notice of the "off-label"

manufacturer's statement, whether true or not–and even mere knowledge of use–can create a new "intended use," and thus a misbranded or adulterated product.

219. The FDA regulations make it plain that it does not regulate the practice of medicine. However the FDA regulations have also made it crystal clear that this is wholly separate and apart from the restrictions the FDA has placed on a manufacturer for promoting or distributing an unapproved product.

> Nothing in this chapter shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient… **Further, this section shall not change any existing prohibition on the promotion of unapproved uses of legally marketed devices.**[100]

220. Therefore, although the FDA does not regulate the practice of medicine,[101] the FDCA does prohibit a manufacturer from promoting a use of the product that is not the specified approved use.[102]

221. Should a manufacturer wish to market a device "for a new or different indication for use, the premarket notification submission must include appropriate supporting data to show that the manufacturer has considered what consequences and effects the change, modification, or new use might have on the safety and effectiveness of the device."[103]

**6. FDA Requires Filing a Supplemental PMA for "Off-Label" Uses.**

222. In addition to limiting premarket approval to only those devices and uses demonstrated to be safe **and** effective, the actual stated purpose of premarket approval is "[t]o

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use, but it also highlights how successful the Medtronic Defendants were with their illegal over promotional campaign for "off-label" uses. *See Minneapolis Firefighters*, 278 F.R.D. 454, 456 (D. Minn. 2011) discussed further herein (*see also*, Complaint in *Minneapolis Firefighters*, attached hereto as Exhibit 21).

[100] 21 U.S.C. § 396 (emphasis added).

[101] *Id.*

[102] 21 U.S.C. § 331(a) (effective 2013); see also 21 C.F.R. § 814.80 (providing that a device "may not be … advertised in a manner that is inconsistent with any conditions to approval specified in the PMA approval order for the device.")

[103] 21 C.F.R. § 807.87(g).

ensure the disapproval of PMA's for devices that have not been shown to be safe **and** effective or that do not otherwise meet the statutory criteria for approval."[104]

223. This prohibition in the FDCA is intended to protect patients and consumers by ensuring that manufacturers do not promote devices that are unsafe or ineffective based on the FDA's standards and review.

224. The terms of 21 C.F.R. § 801.4 render any device "adulterated" or "misbranded" when the manufacturer knew or should have known ("knowledge of facts that would give him notice") that the doctor/hospital/etc. to which the device was sold was going to use it in an "off-label" manner. Under 21 C.F.R. § 801.4, the FDA regulations state that "if a manufacturer knows, or has knowledge of facts that would give him notice that a device introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a device which accords with such other uses to which the article is to be put."

225. Consequently, federal law requires that a medical device manufacturer, who has knowledge or even notice of "off-label" use, to provide adequate labeling.

226. The manufacturer must seek "adequate labeling for such a device which accords with such uses to which the article is to be put."[105]

227. If such a device does not have the required "adequate labeling" the medical device is "adulterated" and "misbranded."[106]

228. "Off-label" use is not approved by the FDA as "safe and effective," which approval is a prerequisite to placing any material on the labeling concerning any use. A manufacturer must seek a PMA supplement for the new, unapproved, "off-label" use.

[104] 21 C.F.R. § 814.2.
[105] 21 C.F.R. §801.4
[106] 21 U.S.C. §352

229. 21 C.F.R. § 814. 39(a) (2012) requires a manufacturer to file a PMA Supplement for changes that affect the safety or effectiveness of a device. This section expressly requires that a manufacturer file a PMA for any "new indications for use of the device." This is not a permissive choice, but rather a federally mandated requirement, as shown by the use of the term "**shall**" in the federal regulation.

230. "After the FDA's approval of a PMA, an applicant **shall** submit a PMA Supplement for review and approval by FDA before making a change affecting the safety or effectiveness of the device for which the applicant has an approved PMA … While the burden for determining whether a supplement is required is primarily on the PMA holder, **changes for which an applicant shall submit a PMA supplement include, but are not limited to, the following types of changes if they affect the safety or effectiveness of the device**: (1) **New indications for use of the device** (2) **Labeling changes**…"[107]

231. A manufacturer must submit a PMA Supplement to the FDA for review/approval changes affecting safety and effectiveness of a device (specifically including new indications);[108] if a manufacturer desires to market or distribute a device "for a new or different indication for use, the premarket notification must include appropriate data to show the manufacturer has considered what consequences and effects the change, modification, or new use might have on the safety and effectiveness of the device."[109]

232. If a manufacturer wishes to obtain approval for a new or different intended use, the manufacturer must go through a lengthy and expensive process to obtain FDA approval for the new use, either by filing a PMA Supplement application pursuant to § 814.39, or by filing a new PMA application.

[107] *See* 21 C.F.R. § 814.39(a) "PMA Supplements" (emphasis added).
[108] 21 U.S.C. § 814.39(a).
[109] 21 C.F.R. § 807.87(g).

233. Any changes the manufacturer believes could affect the safety and effectiveness of the device, including any intention to promote the device for new, unlabeled uses, must be submitted, via a "PMA Supplement," to the FDA for approval. "After FDA's approval of the PMA, an applicant shall submit a PMA supplement for review and approval by FDA before making a change affecting the safety and effectiveness of the device for which the applicant has an approved PMA… While the burden for determining whether a supplement is required is primarily on the PMA holder, changes for which an applicant *shall* submit a PMA supplement include, but are not limited to, the following types of changes if they affect the safety or effectiveness of the device: (1) *New indications for use of the device*…"[110]

**7. FDA Prohibits Misleading or False Promotion and Marketing.**

234. Under the FDCA and FDA's implementing regulations, labeling, promotional advertisements, and making claims about medical devices are deemed misleading if they fail to disclose certain information about the product's risks.[111]

235. Generally, to comply with the FDCA and FDA's implementing regulations, and therefore the PMA, such promotional pieces: (a) Cannot be false or misleading in any particular;[112] (b) Must reveal material facts about the product being promoted, including facts about the consequences that can result from use of the product as suggested in the promotional piece;[113] and, (c) Must be about only approved intended uses.[114]

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[110] 21 C.F.R. § 814.39(a) (emphasis added).
[111] Infuse® was initially approved as a combination medical product which contained a device (the LT-Cage) and a collagen sponge soaked with rhBMP-2 (a Biologic/Device). The FDA classified this combination product as a medical device. Medtronic often sold the collagen sponge soaked with rhBMP-2 (drug) separately from the LT-Cage (the device).
[112] Drugs and devices are misbranded under the Act if their labeling is false or misleading in any particular. 21 U.S.C. § 352(a).
[113] 21 U.S.C. § 321(n); 21 C.F.R. § 1.21.
[114] 21 C.F.R. § 801.4.

236. The FDA regulates the manufacture, sale, and distribution of medical devices in the United States under the authority of the FDCA. This authority includes oversight of labeling and advertising for all medical devices.[115]

237. A medical device shall be deemed to be misbranded if its labeling is false or misleading in any particular.[116] Labeling or advertising may be considered misleading if it fails to reveal material facts about the product being promoted, including facts about the consequences that can result from use of the product as suggested in a promotional piece.[117] "In the case of any restricted device distributed for sale in any State, if (1) its advertising is false or misleading in any particular, or (2) it is sold, distributed, or used in violation of regulations prescribed under section 360j(e),"[118] the device may be consider "misbranded."

238. Advertisements for restricted devices must include "a brief statement of the intended uses of the device and relevant warnings, precautions, side effects, and contraindications…"[119]

239. Restricted device advertisements must not be false or misleading[120] and must reveal facts that are material about the product being advertised, including facts about the consequences that can result from use of the product as suggested in an ad.[121]

**8. General Reporting to The FDA is required after the PMA Process.**

240. A Medical device manufacturer's obligations do not end with the FDA's Premarket Approval ("PMA") process.

[115] *See* 21 U.S.C. § 352(a), (n), (q), & (r).
[116] 21 U.S.C. § 352(a).
[117] *See* 21 U.S.C. § 321(n).
[118] 21 U.S.C. §352(q).
[119] *See* 21 U.S.C. § 352(r)(2).
[120] 21 U.S.C. § 352(q)(1).
[121] 21 U.S.C. § 321(n).

241. Even after premarket approval issues, manufacturers are required to report to the FDA "no later than 30 calendar days after the day: the manufacturer receive[s] or otherwise become[s] aware of information, from any source, that reasonably suggests that a device" marketed by the manufacturer: (a) May have caused or contributed to death or serious injury; or, (b) Has malfunctioned and this device or a similar device [likewise marketed by the manufacturer] would be likely to cause or contribute to a death or serious injury, if the malfunction were to recur.[122]

242. In addition, manufacturers are required to make periodic reports to the FDA regarding approved devices, such reports to include summaries of: (a) Unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices and known to or that reasonably should be known to the applicant; and, (b) Reports in the scientific literature concerning the device and known to or that reasonably should be known to the applicant.[123]

243. Once the FDA has approved a medical device through the PMA application process (such as Infuse®), the manufacturer/applicant is required to comply with the standards set forth in the PMA approval letter. "A device may not be manufactured, packaged, stored, labeled, distributed, or advertised in a manner that is inconsistent with any conditions to approval specified in the PMA approval order for the device."[124]

244. Under federal law, a medical device manufacturer has a continuing duty to monitor the product after premarket approval and to discover and report to the FDA any

[122] 21 C.F.R. § 803.50(a); *see also* 21 U.S.C. § 360i(a) (further detailing the post approval reporting requirements applicable to device manufacturers).
[123] 21 C.F.R. § 814.84(b)(2).
[124] 21 C.F.R. § 814.80.

complaints about the product's performance and any adverse health consequences of which it became aware and that are or may be attributable to the product.

245. Following approval, a medical device manufacturer is required to report adverse events associated with the use of the product, *i.e.* those that may have caused serious injury or death or has malfunctioned and would likely cause or contribute to death or serious injury if recurred.[125]

246. The medical device manufacturer is required to report any incidents or information that reasonably suggests that the device: (a) "[m]ay have caused or contributed to a death or serious injury;" or, (b) "[h]as malfunctioned" in a manner that would likely "cause or contribute to a death or serious injury" if it recurred.[126]

247. "*Each manufacturer shall review and evaluate all complaints to determine whether an investigation is necessary.* When no investigation is made, the manufacturer shall maintain a record that includes the reason no investigation was made and the name of the individual responsible for the decision not to investigate."[127]

248. "*Any complaint involving the possible failure of a device, labeling, or packaging to meet any of its specifications shall be reviewed, evaluated, and investigated*, unless such investigation has already been performed for a similar complaint and another investigation is not necessary."[128]

249. "Any complaint that represents *an event which must be reported to FDA* under part 803 of this chapter shall be promptly reviewed, evaluated, and investigated by a designated individual(s) and shall be maintained in a separate portion of the complaint files or otherwise

[125] 21 C.F.R. § 803.50(a); 21 U.S.C. § 360i(a).
[126] 21 C.F.R. § 803.50(a); 21 U.S.C. § 360i(a).
[127] 21 C.F.R. § 820.198(b). (Emphasis added.)
[128] 21 C.F.R. §820.198(C). (Emphasis added.)

clearly identified. In addition to the information required by 820.198(e), records of investigation under this paragraph shall include a determination of: (a) Whether the device failed to meet specifications; (b) Whether the device was being used for treatment or diagnosis; and, (c) *The relationship, if any, of the device to the reported incident or adverse event.*"[129]

250. Another general reporting requirement for Class III medical devices after PMA approval is that the manufacturer is obligated to inform the FDA of new clinical investigations or scientific studies concerning the device about which the manufacturer knows or reasonably should know.[130] Further, the FDCA subjects approved devices to reporting requirements.[131] For example, the manufacturer must update the FDA when it learns of investigations or scientific studies concerning its device[132], or incidents where the device used in any manner "[m]ay have caused or contributed to a death or serious injury," either due to malfunction or normal operation.[133] The FDA can revoke its approval based on these post-approval reports.[134] The manufacturer must establish internal procedures for reviewing complaints and event reports.[135]

251. Medical device manufacturers are required by federal regulation to "establish and maintain" an adverse event database.[136]

**9. A Manufacturer Must Follow Current Good Manufacturing Practices.**

252. Under 21 C.F.R. § 820.1(a) (2012) of the Quality System (QS) Regulation for Medical Devices, current good manufacturing practice (cGMP) requirements are set forth in this quality system regulation. The requirements in this part govern the methods used in, and the

[129] 21 C.F.R. §820.198(d). (Emphasis added.)
[130] 21 C.F.R. § 814.84(b)(2).
[131] 21 U.S.C. § 360i.
[132] 21 C.F.R. § 814.84(b)(2).
[133] *Id.* § 803.50(a).
[134] 21 U.S.C. §§ 360e(e)(1), 360h(e).
[135] 21 C.F.R. § 820.198(a).
[136] *See* 21 C.F.R. § 803.1(a).

facilities and controls used for, the design, manufacture, packaging, labeling, storage, installation, and servicing of all finished devices intended for human use. The requirements in this part are intended to ensure that finished devices will be safe and effective and otherwise in compliance with the FDCA. This part establishes basic requirements applicable to manufacturers of finished medical devices.

253. 21 C.F.R. § 820.5 "Quality Systems", the FDA regulations state, "Each manufacturer shall establish and maintain a quality system that is appropriate for the specific medical device(s) designed or manufactured, and that meets the requirements of this part."

254. 21 C.F.R. § 820.30(i): "Design controls" states: *Design changes.* Each manufacturer shall establish and maintain procedures for the identification, documentation, validation or where appropriate verification, review, and approval of design changes before their implementation.

255. 21 C.F.R. § 820.30(g): *Design validation* means establishing by objective evidence that device specifications conform with user needs and intended use(s) and "shall include testing of production units under actual or simulated use conditions."

256. 21 C.F.R. § 820.22: "Quality Audit" states: "Each manufacturer shall establish procedures for quality audits and conduct such audits to assure that the quality system is in compliance with the established quality system requirements and to determine the effectiveness of the quality system."

257. 21 C.F.R. § 820.160(a) (2012): "Distribution" states: "**Each manufacturer shall establish and maintain procedures for control and distribution of finished devices to ensure that only those devices approved for release are distributed**...." (Emphasis added.) In other words, a manufacturer is only permitted to distribute a medical device that is approved.

Therefore, if a medical device is going to be used for a use outside of the approved intended uses, then the manufacturer is not permitted to distribute it.

258. 21 C.F.R. § 820.170(a): "Installation" states: Each manufacturer of a device requiring installation shall establish and maintain adequate installation and inspection instructions, and where appropriate test procedures. Instructions and procedures shall include directions for ensuring proper installation so that the device will perform as intended after installation. The manufacturer shall distribute the instructions and procedures with the device or otherwise make them available to the person(s) installing the device.

259. 21 C.F.R. § 803 (2012) states: Manufacturers must include information that is reasonably known to the manufacturer, timely make Medical Device Reporting ("MDR") submissions, define the procedures for implementing corrective and preventative actions, and review sampling methods for adequacy of their intended use.

260. 21 C.F.R. § 820.100 "Corrective and Preventive Action" states: (a) [e]ach manufacturer shall establish and maintain procedures for implementing corrective and preventive action. The procedures shall include requirements for:

a. Analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems. Appropriate statistical methodology shall be employed where necessary to detect recurring quality problems;

b. Investigating the cause of nonconformities relating to product, processes, and the quality system;

c. Identifying the action(s) needed to correct and prevent recurrence of nonconforming product and other quality problems;

d. Verifying or validating the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device; and,

e. Implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems.

**10. Violations of FDA Regulations Void the Federal Preemption Defense.**

261. To the extent, if any, the Infuse® PMA applies to its component parts, manufacturers that promote or distribute their products for "off-label" uses not only are not granted authority to do so by the FDA, but also are not afforded any of the protections or privileges of the FDCA or the MDA, including preemption of any kind or immunity from liability.

262. In light of the Medtronic Defendants' promotion of "off-label" uses – the uses not set forth in the PMA as "intended uses" - the warning approved by the FDA for "on-label", indicated uses was inadequate and harmful to Plaintiffs when they underwent an "off-label" use promoted by Medtronic.[137] In the absence of federal approval of the new intended use(s), there is nothing to preempt state law requirements as the FDA has not reviewed, approved, or passed on those uses not set forth in the premarket application.

263. The Medtronic Defendants' aggressive promotion of Infuse® for "off-label" non-approved uses and obfuscation of the true facts and increased risks and dangers of Infuse®, has led to widespread acceptance among spinal surgeons of such uses as these surgeons mistakenly relied on the Medtronic Defendants to tell them the truth and/or not corrupt the science being published in peer-reviewed medical journals. The Medtronic Defendants' promotion of Infuse® for "off-label" use substantially contributed to Plaintiffs' physicians' use of Infuse® because of these defendants' active promotion of that "off-label" use and their corruption of the published literature. Plaintiffs seek to hold the Medtronic Defendants liable for injuries that trace back to its illegal conduct.

[137] *See* 21 U.S.C. § 352(q), (r).

264. The FDA has not approved the way in which Infuse® was used in Plaintiffs as it was not set forth in the Infuse® PMA and therefore was not an "intended use" and therefore, there were no applicable federal regulations or need to establish a parallel claim.[138]

### E. THE HISTORY OF FDA'S APPROVAL OF INFUSE®

#### 1. The FDA Advisory Committee's Concerns Regarding Off-label Use.

265. The FDA Advisory Committee hearing involving the initial Pre-Market Approval of Infuse® took place on January 10, 2002.

266. The transcript of the hearing makes it clear that the principal concern of the Committee members was that Infuse® *should not be used* in a manner and for uses contrary to the application made by Medtronic for its PMA.

267. Several Committee members expressed profound concern that the use of Infuse® through an approach other than anterior would potentially cause exuberant growth of bone into the spinal canal, thus ossifying the neural elements of the spine and injuring the patient in a significant number of cases. Additionally, Committee members expressed concern regarding the potential cancer risk associated with Infuse®.

268. According to the FDA official transcript of the Committee meeting leading to the initial approval of Infuse® for ALIF procedures only, Committee Member Stephen Li, Ph.D., remarked that nine (9) clinical investigators with a financial interest in the product had reported success with Infuse® more often than investigators without financial interest "almost by a factor of two." The identity of these investigators is not apparent from the transcript.[139]

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[138] Plaintiffs' claims are premised, in part, on Medtronic's "off-label" promotion of Infuse® and the resulting injury. "Off-label" promotion violates federal law. 21 U.S.C. § 331(a); 21 C.F.R. § 814.80.

[139] Orthopedics and Rehabilitation Devices Advisory Panel, at page 288-290, (Jan 10, 2002), *available at* http://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=2&ved=0CDQQFjAB&url=http%3A%2F%2Fwww.fda.gov%2Fohrms%2Fdockets%2Fac%2F02%2Ftranscripts%2F3828t1.doc&ei=YaDuUfXnM5DhiwLaroCgCw&usg=AFQjCNFVP4BHeX9LJOkYgyQCMXcnz8EuMQ&sig2=QLM5gwh4Z

269. The Medtronic Defendants' agents, Thomas A. Zdeblick, M.D., Hallett Matthews, M.D.,[140] and Scott Boden, M.D., three of Medtronic's most highly paid consultants and royalty recipients, were present and testified on behalf of Medtronic at the hearing.

270. Agents Zdeblick, Matthews and Boden assured the Committee (particularly through Medtronic's agent Scott Boden, M.D.) that the only approval sought, *i.e.*, use of Infuse® for the single level lumbar anterior approach, would prevent leakage of the BMP into the neural elements of the spine.[141]

271. During the hearing, panel member Dr. Hanley questioned the sponsored physicians regarding "off-label" use and asked, "[w]e have one question and that relates to one of those letters that was read earlier about putting the BMP adjacent to the nerve for a posterior approach. It doesn't relate to the indication being sought for here but any comments from people on that?"[142]

272. Medtronic's agent Scott Boden, M.D., dismissed this concern by responding:

> [o]bviously, the risks and complications of the device are that of the surgery, the insertion of the cage and what's inside the cage, and this specific application before the panel today is through an anterior approach, either an open or a laparoscopic and to talk about safety issues that are related to a different surgical approach seems to me to be outside the scope of what we ought to be focusing on today.[143]

273. At the time of this hearing, the Medtronic Defendants' agent Thomas A. Zdeblick, M.D. was a consultant for Medtronic, making $400,000 per year for eight (8) days of consulting (not including "royalties" he received from the Medtronic Defendants).

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9143xAkeCxgcw&bvm=bv.49478099,d.cGE, (attached hereto as Exhibit 22).

[140] John Fauber, *Medtronic Helped Write, Edit Positive 'Infuse' Spine Studies*, Milwaukee Journal Sentinel/MedPage Today (October 2012), attached hereto as Exhibit 23, also *available at* http://www.medpagetoday.com/PainManagement/BackPain/35551,.

[141] Exhibit 22, Orthopedics and Rehabilitation Devices Advisory Panel, at page 73, et seq.

[142] *Id.* at 243.

[143] *Id.*

274. At the time of this hearing, the Medtronic Defendants' agent Scott Boden, M.D. was receiving at least $100,000 per year in consulting fees from Medtronic (not including "royalties" he received from Medtronic).

275. At the time of this hearing, the Medtronic Defendants' agent Hallett Mathews, M.D. was making an average of at least $250,000 per year in consulting fees from Medtronic.

276. At the time of this hearing, the Medtronic Defendants' agents Dr. David Polly, J. Kenneth Burkus, M.D., and Charles Branch, M.D. were all listed by Medtronic as *resources* for this hearing, and were presumably present, but did not speak (all received significant consulting and/or royalty payments from Medtronic) as discussed herein *supra*.

277. Six months following the initial hearing, the Committee on July 2, 2002, voted to approve Infuse®, *but only with the tapered LT-Cage in a single level lumbar anterior approach.* Any surgical approach other than the anterior requires the posterior barrier to the spinal canal to be intentionally compromised and such was not approved.

278. Following obtaining the FDA approval of Infuse® for a specific intended use, the Medtronic Defendants' agents Scott Boden, M.D., Thomas A. Zdeblick, M.D. and J. Kenneth Burkus, M.D. actively worked to promote the BMP/Sponge within the medical community, for uses and in a manner contrary to the restrictions in the Infuse® PMA.

279. During such period of time, the Medtronic Defendants' agents Scott Boden, M.D., Thomas A. Zdeblick, M.D. and J. Kenneth Burkus, M.D. failed to make adequate, if any, disclosure of their relationship or compensation from these defendants.

280. During such period of time, the FDA approved use of Infuse® only had an extremely small share of the fusion market.

281. The Medtronic Defendants' agent Scott Boden, M.D. received compensation from

these defendants between 1996 and 2010 of $28,796,034.00.

282. During such period of time, Medtronic Defendants' agent Scott Boden, M.D. wrote extensively on the use of the BMP/Sponge, when combined with Class II surgical cages untested and unapproved for use with a biologic.

283. By way of example and not limitation, the Medtronic Defendants' agent Scott Boden, M.D. wrote that use of the BMP/Sponge is likely to be effective even for uses and in a manner contrary to the Infuse® PMA. His article in *Orthopedic Nursing*, also praises the benefits of the product, noting that while the BMP/Sponge "is quite expensive, [its] potential to lessen morbidity, accelerate healing and provide more consistent results undoubtedly justify these costs in appropriately selected patients."[144]

284. By way of example and not limitation, the Medtronic Defendants' agent Scott Boden, M.D. along with Drs. Paul A. Anderson, Keith H. Bridwell, and Jeffrey C. Wang, authored a July 2007 article in the *Journal of Bone and Joint Surgery*, titled "What's New in Spine Surgery." The article discussed, among other things, a study that examined the use of the BMP/Sponge in a Posterolateral Fusion procedure, contrary to the ALIF approved by the Infuse® PMA. According to the authors, the study reported that BMP improved fusion rates when used in combination with iliac crest bone graft in an unapproved procedure in which the rhBMP-2 was wrapped around local bone as a bulking agent.[145]

285. During such period of time, the Medtronic Defendants' agent Thomas A. Zdeblick, M.D., the Chairman of the Department of Orthopedics and Rehabilitation at the University of Wisconsin, failed to properly disclose his financial relationship with these defendants.

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[144] Scott Boden, *The ABC's of BMPs*, 24 Ortho. Nursing, 49-52 (2005) (attached hereto as Exhibit 24).
[145] Scott Boden, et al., *What's New in Spine Surgery*, J Bone Joint Surg Am. 92(10):2017-28 (2010) (attached hereto as Exhibit 25).

286. The only disclosure made by the Medtronic Defendants' agent Thomas A. Zdeblick, M.D. were annual payments exceeding $20,000 in University conflict of interest forms when, in truth and in fact, he actually received between $2.6 and $4.6 million per year.

287. The Medtronic Defendants paid their agent Thomas A. Zdeblick, M.D. an annual salary of $400,000 under a contract that only required him to work eight (8) days per year.[146]

288. The Medtronic Defendants' agent Thomas A. Zdeblick, M.D. received $34,168,739.81 from Medtronic between 1996 and 2010.[147]

289. Medtronic's agent Thomas A. Zdeblick, M.D. also has been a significant contributor to the Medtronic Defendants' promotion of BMP, authoring seven peer-reviewed articles on BMP and appearing as a presenter at medical conferences and symposia in which the topics included discussion of uses of BMP, the BMP/Sponge and/or use in combination with Class II medical devices, untested and FDA-unapproved for such purposes.

290. Only a few months after Infuse® was approved, the Medtronic Defendants' agent Thomas Zdeblick, M.D. authored a 2003 paper where he declared that BMP could become "the new gold standard" in spine surgery and added that it was being used "exclusively" at his institution. The paper was published in the *Journal of Spinal Disorders & Techniques*, where Zdeblick is the editor-in-chief, but failed to mention that Dr. Zdeblick received significant royalties on the Medtronic LT-Cage, which is the 2nd component of Infuse®.

291. On the website, www.Back.com, which is owned and operated by Medtronic, Medtronic's agent Thomas A. Zdeblick, M.D. describes the advantages of BMP and appears in an online video discussing the benefits of the product which he claims includes no adverse

[146] *Medtronic Paid Researcher More than $20,000 – Much More*, The Wall Street Journal (Jan 16, 2009) (attached hereto as Exhibit 26).
[147] Exhibit 27, U.S. Senate, Committee on Finance (October 2013), *Staff Report on Medtronic's Influence on Infuse Clinical Studies*, at 5.

events. Conspicuously, the video only discusses spinal surgery from the *posterior* approach of the spine, a procedure contrary to the restrictions in the Infuse® PMA, and fails to discuss or provide any merit to the approved approach. In this video Medtronic's agent Thomas A. Zdeblick states "we looked at the safety concerns with Infuse® very carefully and did not find any adverse events, it's a naturally occurring protein and well accepted by patients." (Emphasis added.)

292. The Medtronic Defendants' agent J. Kenneth Burkus, M.D., is an orthopedic surgeon and a self-described "consultant" for Medtronic.

293. Medtronic's agent J. Kenneth Burkus, M.D. received $6,380,336.83 from the Medtronic Defendants between 1996 and 2010.[148]

294. During such period of time, the Medtronic Defendants' agent J. Kenneth Burkus, M.D. was the lead author of four of the original thirteen studies of Infuse® sponsored by these defendants.[149]

295. All of the studies by the Medtronic Defendants' agent, J. Kenneth Burkus, M.D., failed to report any of the observed adverse events that were subsequently revealed by a recent independent review of his data and the publication of the misleading and false results discussed hereinafter.

**2. FDA Restricted the Approved Use because of Safety Concerns**

296. The FDA reviewed Infuse®'s safety and effectiveness only for the uses the

[148] *Id.*

[149] Burkus JK, Gornet, MF, Dickman CA, Zdeblick TA, *Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages*, J. Spinal Disord. Tech, 2002; 15:337-49; Burkus JK, Transfedlt EE, Kitchel SH, et al., *Clinical and radiographic outcomes of anterior lumbar interbody fusion using recombinant human bone morphogenetic protein-2*, Spine 2002; 27:1219-24; Burkus JK, Sandhu HS, Gornet MF, Longely MC, *Use of rhBMP-2in Combination with Structural Cortical allografts surgery: clinical and radiographic outcomes in anterior lumbar spinal fusion*, J. Bone Joint Surg. Am. 2005;87:1205-12; and Burkus JK, Heim SE, Gornet MF, Zdeblick TA, *Is INFUSE bone graft superior to autograft bone? An integrated analysis of clinical trials using the LT-CAGE lumbar tapered fusion device*, J. Spinal Tech. 2003;16:113-22. (Also attached hereto as Exhibit 28.)

Medtronic Defendants specified in their PMA application and the regulations are premised on that specific review.[150]

297. As presented in the Medtronic Defendants' original PMA application, which was eventually approved by the FDA on July 2, 2002, Infuse® consists of two components: (1) the tapered LT-CAGE Lumbar Tapered Fusion Device Component, a thimble-sized hollow metal cylinder that keeps the vertebrae in place and provides a frame that contains and directs the development of new bone growth; and (2) The Infuse® Bone Graft Component, which includes an Absorbable Collagen Sponge ("ACS") that acts as a carrier and scaffold for the active ingredient in Infuse®, and rhBMP-2, the actual active ingredient that is reconstituted in sterile water and applied to the ACS.

298. Although these two components are sold separately, the initial approved labeling for the product indicates that Infuse® requires both components.

299. The approved labeling for the product reads in part, with bold and underlined formatting: **"These components must be used as a system. The Infuse® Bone Graft component must not be used without the LT-Cage Lumbar Tapered Fusion Device component."**[151] (Emphasis added.)

300. The labeling also directs the specific manner in which both components are to be used in a fusion procedure.

301. Infuse® was initially approved by the FDA for exclusive use in the lower lumbar region of the spine (at levels L4 through S1), via an anterior approach (where the spine is

[150] 21 U.S.C. § 360c(a)(2) (stating that the FDA measures the "safety and effectiveness of a device… with respect to the conditions of use prescribed, recommended, or suggested in the labeling of the device, and weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use."); *id.* § 360e(c)(1) (2012).
[151] Infuse® Label, Exhibit 2.

approached by going in through the patient's abdomen), and only at one level per surgery.[152]

302. Infuse® was **NOT** approved for any other surgical approach or for use in any other region of the spine.[153]

303. The original PMA Approval Letter dated July 2, 2002 from the FDA to Richard Treharne, Ph.D. Senior Vice President of Regulatory Affairs, provides in part that the approval of Infuse® is strictly limited as follows:

> The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 C.F.R 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that, to ensure the safe and effective use of the device, **the device is further restricted within the meaning of section 520(e)** under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of a practitioners who may use the device as approved in this order and (2) **insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act**.[154] (Emphasis added).

304. The PMA Approval Letter also provides in part as follows:

> [i]n addition to the post-approval requirements outlined in the enclosure, you have agreed to provide the following data in a post approval report: 1. In order to assess the long-term performance of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar tapered Fusion Device, please conduct a post-approval study to obtain a total of 6 years of postoperative data from a statistically-justified number of patients implanted with this device…2. Because of unknown long-term device performance, particularly the resulting bony fusion characteristics, the post approval study should also contain retrieval analyses of any InFUSE™ Bone

[152] The FDA approval letter specifically states, "[t]his device is indicated for spinal fusion procedures in skeletally mature patients with degenerative disc disease (DDD) at one level from L4-S1…InFUSE™ Bone Graft/LT -CAGE™ devices are to be implanted via an anterior open or an anterior laparoscopic approach," Approval Letter from the FDA to Medtronic Vice President Richard Treharne, Ph.D. regarding PMA Approval (July 2, 2002), Exhibit 1.

[153] Although the Infuse® label remains substantially the same as that approved by the FDA in 2002, the FDA did make minor adjustments to the label through post-approval supplements and the granting of additional PMAs. For example, on July 29, 2004, the FDA approved a supplement expanding the indicated spinal region from L4-Sl to L2-Sl. The BMP/Sponge combination device was also approved by the FDA, via new PMAs, to be used in maxillofacial procedures on March 9th, 2007 and in April of 2004 for repair of tibial fractures. (See Exhibits 12 and 11.)

[154] Letter from the FDA to Medtronic Vice President Richard Treharne, Ph.D. regarding PMA Approval (July 2, 2002), Exhibit 1; It should be noted that Infuse® was approved as a "restricted device" within the meaning of the ACT.

> Graft/LT-CAGE™ Lumbar Tapered Fusion Device that is implanted and subsequently removed. This section is not limited to the patient population as described in item 1 above…3. Perform post-approval studies, which assess the effects of rhBMP-2 on tumor promotion…4. Perform post-approval studies to investigate the potential for an immune response to rhBMP-2 to interfere in embryonic development in rabbits. Observation from this investigation may indicate a necessity to create a pregnancy monitoring database and/or modify your labeling.

305. The PMA was accompanied by an attachment setting forth the general "CONDITIONS OF APPROVAL."

306. These general conditions (applicable to all Class III approved devices during 2002) require that Medtronic submit a PMA supplement "when unanticipated adverse effects, increase in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification."[155]

307. These general conditions require Medtronic to provide a 'Special PMA Supplement – Changes Being Effected.'

308. These general conditions specify that such supplement "is limited to the labeling, quality control and manufacturing process changes specified under 21 C.F.R. 814.39(d)(2) (2012). It allows for the addition of, but not the replacement of previously approved, quality control specification and test methods. These changes may be implemented before FDA approval upon acknowledgment by the FDA that the submission is being processed as a 'Special PMA Supplement – Changes Being Effected.' This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source."[156]

309. The general "Conditions of Approval" section of the PMA also sets forth in part that "[c]ontinued approval of this PMA is contingent upon submission of post-approval reports

[155] Approval Letter, Exhibit 1.
[156] *Id*

required under 21 C.F.R. 814.84 (2012) at intervals of 1 year from the date of approval of the original PMA."[157]

310. Such post-approval reports must include "a. unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices includes devices which are the same or substantially similar to the applicant's device); and b. reports in the scientific literature concerning the device."[158]

311. Additionally, the PMA contains requirements concerning the Medtronic Defendants' reporting of adverse reactions and device defect.

312. The Medtronic Defendants, pursuant to the general conditions of approval, are required to provide the FDA within 10 days of receiving or having knowledge of information concerning: "[a]ny adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and; a. has not been addressed by the device's labeling; and b. has been addressed by the device's labeling but is occurring with unexpected severity or frequency."[159]

313. The general "Conditions of Approval" section of the PMA provided, in part that Medtronic must comply with The Medical Devices Reporting Regulation and "report to the FDA whenever they receive or otherwise become aware of information, from any source, that reasonably suggests that a device marketed by the manufacturer or importer: 1. May have caused or contributed to a death or serious injury; or 2. Has malfunctioned and such device or similar device marked by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur." [160]

[157] *Id.*
[158] *Id.*
[159] *Id.*
[160] *Id.*

314. The PMA for Infuse® was expressly conditioned upon the Medtronic Defendants' compliance with and satisfaction of the above general conditions and requirements.

315. The FDA made clear in the PMA that "**[f]ailure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act**."[161] (Emphasis added).

316. Neither Infuse® nor any of its component parts has ever been approved by the FDA for use in other parts of the spine or for use in any other type of spinal procedure.[162] Therefore, all other uses are "off-label" and unapproved uses.

317. Physicians may use FDA-approved medical devices in any way they see fit, but the manufacturer is not permitted to promote in any way a medical device for uses other than the "intended uses" as set forth in the PMA application.

318. The promotion by a medical device manufacturer for any "off-label" or unapproved uses for its devices or payment to doctors as inducements or kickbacks so that they promote "off-label" uses is strictly unlawful and in violation of the PMA and federal regulations.

319. The Medtronic Defendants have aggressively over-promoted, as well as induced, uses other than "indicated uses" of the component parts of Infuse®.

320. Such over-promotion for uses other than "indicated uses" was a violation of the "CONDITIONS OF APPROVAL."

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[161] *Id.*

[162] As further discussed herein, the FDA, in March of 2011, rejected Medtronic's application for Amplify, which is another rhBMP-2 bone growth protein used in Infuse® *see* Russolillo, Steven, *FDA Rejects Medtronic Spine Device,* Wall Street Journal (March 2011) (attached hereto as Exhibit 29) (emphasis added); Amplify contained three times the amount of rhBMP-2 found in Infuse®. The FDA reviewers stated "[t]he primary safety concern is the increased numbers of cancer events in patients treated with Amplify compared to the control group." Richwine, Lisa, *FDA staff: Cancer a concern with Medtronic device*, Reuters (July 2010), attached hereto as Exhibit 30, also *available at* http://mobile.reuters.com/article/healthNews/idUKTRE66M2U820100723.

### 3. After PMA Approval, Medtronic Published a False "Fact Sheet"

321. Following the FDA approval of Infuse® restricting its use, the Medtronic Defendants published a "Fact Sheet". The Fact Sheet falsely represented, in part, the following:

> **Fact Sheet**
>
> ***INFUSE® Bone Graft/LT-CAGE®*** Lumbar Tapered Fusion Device… Spinal fusion surgery with INFUSE® Bone Graft and the LT-CAGE® Device **is essentially the same as traditional autograft procedures**, without the need for the additional surgery to harvest bone from the patient's hip. **Scientists determined** that rhBMP-2, with an absorbable collagen sponge as the carrier, (INFUSE® Bone Graft) **is an effective replacement for autograft bone in spinal fusion surgery**. This conclusion is **based on data resulting from a large-scale, multi-center, prospective, randomized, two-year study** involving 279 degenerative disc disease patients implanted with INFUSE® Bone Graft and the LT-CAGE® Lumbar Tapered Fusion Device. The **study assessed the safety, efficacy** and therapeutic benefits of the new procedure as compared to traditional autograft procedures… The data showed that the study met all of its primary endpoints… Long-term cost offsets (within two years of surgery): **Significantly fewer complication**s that would require follow-up visits…[163] (emphasis added).

322. In the "Fact Sheet," the Medtronic Defendants made representations that Infuse® is essentially the same autograft procedures.

323. In the "Fact Sheet" the Medtronic Defendants state; "The **study assessed the safety, efficacy** and therapeutic benefits of the new procedure as compared to traditional autograft procedures… The data showed that the study met all of its primary endpoints… Long-term cost offsets (within two years of surgery): **Significantly fewer complication**s that would require follow-up visits…."[164]

324. The Medtronic Defendants did not reveal that its employees significantly altered the printed/reported results of those "studies" to reflect better outcomes for the BMP/Sponge and worse outcomes for the alternative procedures, than what was in truth observed.

325. Nor did Medtronic Defendants disclose that **these "scientists" were extremely**

[163] Medtronic, Fact Sheet (2002), Exhibit 31 (emphasis added).
[164] *Id.*

**highly compensated** by Medtronic to the tune of millions and in some cases, tens of millions of dollars or that Medtronic employees actively edited, participated in the creation of, and/or **ghostwrote the text used in the published study**.

### F. INFUSE® USES OTHER THAN PMA APPROVED ARE 'OFF-LABEL'

#### 1. Description of "On-label" and "Off-label" Infuse® Uses

326. To be considered an ***on***-label use, Infuse® must be applied as follows: (a) BMP is impregnated on a supplied absorbable collagen sponge that is inserted inside an FDA approved Medtronic cage - the L-T Cage;[165] (b) This cage is placed via anterior approach; (c) Only a single level is fused; and, (d) The fusion is performed between the L2 and S1 levels of the spine.

327. If any one of these criteria is violated, the FDA has not approved the use of Infuse® or any of its components.

328. There are many ways in which the components of Infuse® may be used for a use or in a manner unapproved by the FDA.

329. Generally speaking, BMP can be placed in three locations: inside an interbody cage, surrounding the cage within the disc space, and along the posterior elements of the spine.

330. Only the approved L-T Cage can be used; therefore, the use of any other cage constitutes an FDA-unapproved use of Infuse® and its components.

331. There are numerous models of cages manufactured by a variety of companies. An incomplete list of the most noted "off-label" models includes cages manufactured by Medtronic, Depuy Lordotic Cages, Stryker Interbody Fusion Cages, NuVasive Spine Cages, and Zimmer

[165] The FDA has only approved the LT-CAGE Lumbar Tapered Fusion Device (LT-Cage) and the Inter Fix Threaded Fusion Device for use with Infuse® in Spinal Fusions, *see* http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=2344 (also attached hereto as Exhibit 32); The FDA also approved Mastergraft with the use of Infuse® for a humanitarian exception which was later withdrawn at the request of Medtronic in 2010, *available at* http://www.fda.gov/medicaldevices/productsandmedicalprocedures/deviceapprovalsandclearances/hdeapprovals/ucm161827.htm (also attached hereto as Exhibit 33) (emphasis added).

Interbody Fusion PEEK Cages.[166] These are all Class II devices that have not been approved for use with the BMP component of Infuse®.

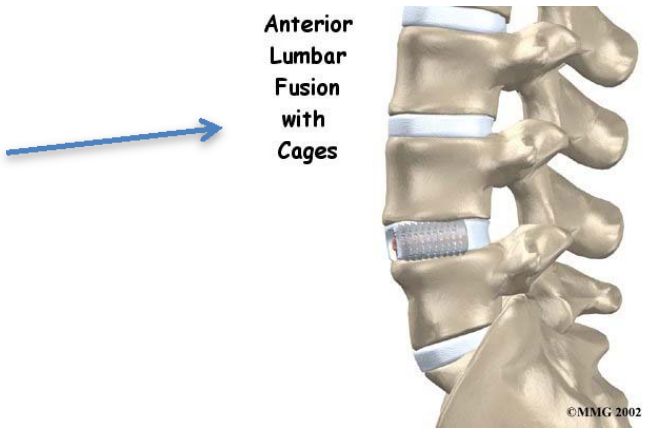
332. If BMP is directly placed in the space between two vertebrae, the surgeon's operative report will commonly refer to placing BMP in the anterior disc space prior to inserting a cage. Similarly, BMP can be applied laterally or posteriorly to the cage after insertion of the cage.

333. The surgeon has a number of choices when selecting a surgical approach for cage insertion in an interbody fusion. The most common of these are the anterior approach, the posterior approach, the transforaminal approach, and the extreme lateral approach.

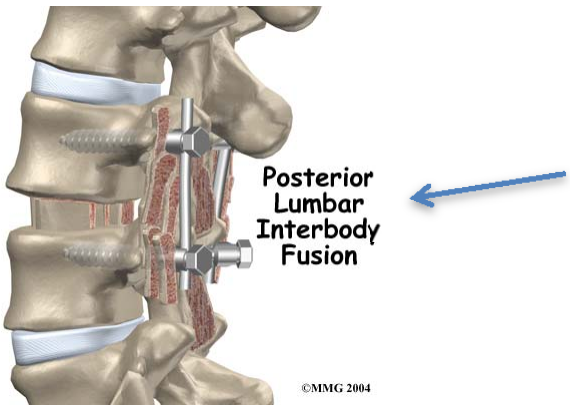
334. When adopting an anterior approach, the surgeon makes an incision in the abdomen with the patient in a supine (face-up) position. He or she proceeds to insert the cage

[166] Per Counsels' investigation, additional cages include but are not limited to the following cages: Allograft Strut; Alphatec; Alphatec Novel; Alphatec PEEK; Alphatec Spine; Alphatec Zodiak; Altiva ArcTec LT; AVS Interbody; Axial Cage; AxiaLIF Cage; BAK; Bak Titanium Cage; Banana; Bengal Cage; Biomechanical Cage; Biomet PEEK; Biomet Solitaire PEEK; Blackstone; Blackstone PEEK Cage; Boomerang; Brantigan Carbon Fiber Cages; Bullet; Carbon Bullet Cage; Clydesdale Cage; Concord; Cornerstone; CoRoent; Crescent; Crosslink Medium; Custom Machine Biomechanical Femoral Allograft Prosthetic Space; Depuy; Depuy Acromed; DePuy Acromed Cage; DePuy Allograft Spacers; DePuy Anterior Lordotic Carbon Fiber Cages; DePuy Carbon Fiber Cage; Depuy Concode Bullet Cage; DePuy Cougar; DePuy Leopard; DePuy Lordotic Cage; Depuy Saber – PEEK; Femoral Ring Allograft; Geo; Global; Globus; Graftech Anterior Ramp; Harms Cage; Hollywood Interbody Fusion Device; HSR Graft; Hydrasorb Type Spacer; IC Graft Chamber; Implex; Infinity; InFix Innovasis X Box Cages; Innovasive; Innovation PEEK; Ionic; Ladotic; LANX Cage; Laris-Is Anteliys GX PEEK; LDR ROA Cage; Leftnet; Legacy; Life Spine Spacer & Biomet Biologics Spacer; LifePlan Health VG2P; Linxx Peek; Long Vuc-Pod Cages Loop TLIF Cage AMT Loop Interbody Cages; Mesh Cage; Mobis PEEK Spacer; Novel; Nutech; NuVasive; Nuvasive Spine Wave; Nuvasive STD; Synthes CCALIF Biomechanical Device; Ocelot Cage; ODC Implant; Perimeter Cage; Pioneer Bullet; Pyramesh; Rabea 5 Peek; Rattlesnake-Eminent; Ray Cage; Redmed PEEK; Regeneration Tech Threaded Bone Dowel; RTI Biologics Cage; Scientx; Sea Spine PEEK Spacers Seaspine Hollywood; Shadow Mesh; Signature Peak; Signus Tetrus; SinMesh Interbody Cage; Sofamar Boomerang II; Sonoma; Sovereign Cage; Spinal USA Titanium; Spine Frontier; Synthes CCALIF; Spine Metrics PEEK Spacer; Spine Wave Expandable Cage; Spine Wave XD Cartridge; Spinefrontier S-LIFT PEEK Cage; Spineology; Spinewave Staxx XD Cartridge; StaXx - D PEEK Expandable Cage; Stryker; Synfix; Synthes OPAL; Synthes PEEK; T Lift; Tangent; Telemon; Tetris; Theken Interbody Cage; Theken Spine Non-Tapered Cage; Thekenspine Nontapered Cage; Thekon PEEK Spacer; Threaded Bone Dowell; Titan; Titan Endoskeleton; USA Cage System; Ventura;Versa Trac P Cage; Verte Stack; VG2C Lifenet Health; Vitoss; X Core Expandable XLIF Cage – Nuvasive; X2 Crescent PEEK; Zero-P Synthes Spacer; Zimmer Parallel Slotted; Zimmer Ardis P; Zimmer BAK; Zimmer Lucent; and Zimmer PEEK.

through the retroperitoneal space to the front face of the spine. Spinal fusions that use a cage and adopt an anterior approach are called "anterior lumbar interbody fusions" or "ALIFs." When combined with the three other criteria, this is the **only** approach that will constitute an ***on***-label procedure.



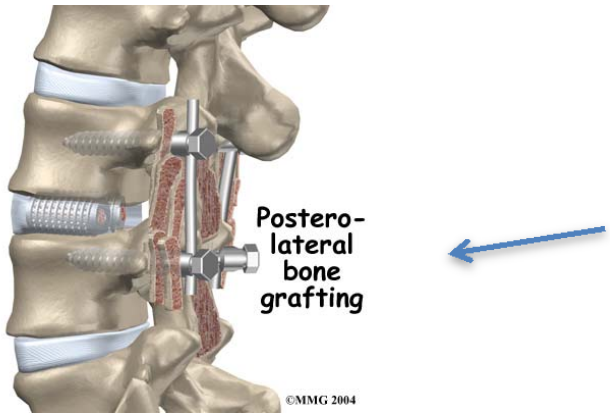

335. A cage (other than the LT-Cage) can be inserted via a posterior approach when an incision is made in the back with the patient in the prone position (faced down). The cage is then implanted into the interbody space from the back face of the spine. This kind of fusion is called a "posterior lumbar interbody fusion" or "PLIF." This is an "off-label" use of Infuse®.




336. A cage (other than the LT-Cage) can be inserted from either the right or left face of the spine by modifying the PLIF. These fusions are called "transforaminal lumbar interbody fusions" or "TLIFs." A TLIF is accomplished by creating an incision in the back, reaching

around the side of the spine, and inserting the cage from either the left or the right. This is "off-label" use of Infuse®.

337. An additional procedure is also considered to be "off-label" when Infuse® is applied along the posterior or posterolateral elements of the spine, including the facet joints, posterolateral gutters, and transverse processes. When Infuse® is placed in any of these posterior elements the surgery is called a "posterior" or "posterolateral" fusion (PLF), and no cage is used.




338. In fact, any use of Infuse®, or any use of its components separately, that was not set forth in the premarket application as the "intended uses" and thereafter approved by the FDA in any of the PMAs or PMA Supplements, is an "off-label" use or is simply use of a medical device, never reviewed or approved by the FDA.

339. The spine consists of four general regions, cervical (neck), thoracic (chest), lumbar (low back), and sacral (lowest portion of the spine). Each region consists of individual vertebras, which are described as "levels." These levels are numbered, with lower values corresponding to the vertebra that lay higher on the spine.

340. The cervical spine consists of seven levels, designated C1-C7. The thoracic spine consists of twelve levels, ranging from T1-T12. The lumbar spine usually consists of five vertebras, ranging from L1-L5. The sacrum is a structure immediately below the lumbar spine and consists of two levels, S1 and S2.

341. To be considered an on-label use, Infuse® must be applied at only one level, from L2-S1 in the lumbar or lumbosacral spine.

342. If Infuse® is used in more than one level, or outside L2-S1, then the FDA considers the procedure to be "off-label" and/or used of a medical device never reviewed or approved by the FDA.

**2. Medtronic's Breach of Its Duty to Seek a Supplemental PMA**

343. The Medtronic Defendants did not seek a post-approval supplement to their PMA or a new PMA to add additional intended uses or have additional components approved for use with the BMP.

344. The Medtronic Defendants did not seek such a post-approval supplement or new PMA because they wanted to avoid the lengthy and time-consuming process.

345. The Medtronic Defendants did not seek such a post-approval supplement or new PMA because they knew that the science would not support their application.

346. The Medtronic Defendants knew or had reason to know that based upon the results of prior Medtronic-sponsored clinical studies of "off-label" uses (which were abruptly terminated as a result of observed complications) that "off-label" uses would be neither safe, nor effective.

347. The Medtronic Defendants knew or had reason to know that for that reason, the supplemental PMA or new PMA would be rejected.

348. Instead, the Medtronic Defendants engaged in very active and concerted efforts to market, promote, and sell the components of Infuse® "off-label" and/or marketed, promoted and sold the components of Infuse® in combinations which were medical devices separate and distinct from Infuse® which had never been approved.

349. In undertaking such effort, the Medtronic Defendants totally disregarded the increased risks, dangers, and complications that these Defendants knew or should have known were associated with "off-label" and/or unapproved uses of the components of Infuse®.

350. The Medtronic Defendants did not notify the FDA of the "off-label" and unapproved uses, as required by federal law.

351. The Medtronic Defendants did not track and report the adverse events associated with the "off-label" and unapproved uses, as required by federal law.

352. The Medtronic Defendants did not seek to strengthen or increase the labeling to warn of the known and/or knowable dangers associated with "off-label" and/or unapproved uses of Infuse®'s parts and components as required by federal law.

353. The Medtronic Defendants did not file a PMA Supplement to seek approval for these unapproved devices and their use.

354. The Medtronic Defendants did not file a new PMA application for the such uses, as required by federal law.

355. The Medtronic Defendants did not discontinue sales of devices when they knew, or had reason to know, such devices were intended for purposes unreviewed and unapproved by the FDA.

356. Contrary to federal law, the Medtronic Defendants did not report the unapproved uses and/or unapproved medical devices to the hospital(s) when these Defendants knew the components of Infuse® were being so utilitzed..

357. The Medtronic Defendants did not act as a reasonably prudent manufacturer of manufacturer of Class III medical devices in the promotion, sale, and distribution of Infuse® and its components.

358. The Medtronic Defendants did not act as reasonably prudent manufacturer of Class II medical devices in the promotion, sale and distribution of its Class II PEEK cages, including P's cages.

359. The Medtronic Defendants continued to illegally promote, market, and sell the the parts and components of Infuse® for unapproved uses in order to reap enormous profits from those sales for use on hundreds of thousands of unsuspecting and vulnerable patients, some of whom would later suffer irreparable, debilitating and life-altering injuries caused by such.

360. The Medtronic Defendants prioritized market share and profit above the health and safety of patents and consumers, above FDA rules and regulations and above state common law duties.

361. The Medtronic Defendants have violated federal law, FDA regulations, their PMA, and state common law duties, breached the trust of physicians and patients who relied on these defendants to act as reasonably prudent manufacturers. The Medtronic Defendants acted in concert with their agents and with other Defendants as set forth herein, and acted in conscious and willful disregard of the health and safety of patients, including Plaintiffs herein..

### G. FDA WARNS SURGEONS OF "OFF-LABEL" USE IN THE CERVICAL SPINE

362. On July 1, 2008, the FDA sent out a public health notification "Dear Doctor" letter regarding the life-threatening complications associated with using Infuse® in cervical spine fusions.

363. In the letter, the FDA stated "[t]his is to alert you to reports of life-threatening complications associated with recombinant human Bone Morphogenetic Protein (rhBMP) when used in the cervical spine. Note that the safety and effectiveness of rhBMP in the cervical spine

have not been demonstrated and these products are not approved by FDA for this use."[167]

364. The FDA further stated: "complications were associated with swelling of the neck and throat tissue, which resulted in compression of the airway and/or neurological structures in the neck. Anatomical proximity of the cervical spine to airway structures in the body has contributed to the seriousness of the events reported and the need for emergency medical intervention."[168]

365. With respect to unknown risks, the FDA stated that "[t]he mechanism of action is unknown, and characteristics of patients at increased risk have not been identified."[169]

366. The FDA warned that BMP was only approved by the FDA for the limited-use of fusions of the lumbar spine, in skeletally mature patients with degenerative disc disease (DDD), at one level from L2-S1.

367. The FDA emphasized that BMP use outside the Infuse® system approved by the FDA is dangerous and "since the safety and effectiveness of rhBMP for treatment of cervical spine conditions has not been demonstrated, and in light of the serious adverse events described above, **FDA recommends that practitioners either use approved alternative treatments or consider enrolling as investigators in approved clinical studies.**"[170]

368. The Medtronic Defendants have resolved at least one wrongful death civil case filed related to the use of BMP in the cervical spine.[171] On August 21, 2008, Shirley Nisbet, a resident of Vista, California, underwent a cervical fusion procedure in which a Medtronic sales

[167] FDA Public Health Notification: Life-Threatening Complications Associated with Recombinant Human Bone Morphogenetic Protein in Cervical Spine Fusion (July 1, 2008), *available at* http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm062000.htm (also attached hereto as Exhibit 34) (emphasis in original).
[168] *Id.*
[169] *Id.*
[170] *Id.*
[171] *Nisbet v. Medtronic*, Case No. 8:08-cv-01361-JVS-RNB (C.D. Calif. [Southern Div.-Santa Ana]) was filed on 12/2/2008 and terminated on 2/27/09 by the filling of a Notice of Voluntary Dismissal w/o Prejudice by plaintiffs.

representative allegedly encouraged and recommended to her surgeon, prior to and during the surgery, that the surgeon use BMP in Ms. Nisbet's cervical spine. Following the operation, Ms. Nisbet had difficulty breathing and swallowing, and experienced severe pain and swelling in her neck. In the following days, her symptoms became progressively worse until her breathing became so compromised due to neck swelling and compression of her airway that she stopped breathing and fell into a coma on August 23, 2008. She remained in a vegetative state but was kept alive by artificial means for several days, until she died on August 30, 2008.[172] It has been reported that Medtronic subsequently settled this wrongful death action.

### H. "OFF-LABEL" SALES ARE VERY PROFITABLE FOR MEDTRONIC

369. Sales of the 1st component of Infuse® have become a blockbuster product for the Medtronic Defendants.

370. BMP/Sponge sales alone were nearly $900 million for the fiscal year of 2011.[173]

371. The Medtronic Defendants have depended heavily on the sales of the BMP/Sponge because their sales in other market areas, such as cardiac defibrillators, have significantly slowed due to numerous product recalls of a wide-variety of defective products for these defendants.

372. The Medtronic Defendants' reliance on BMP/Sponge for sales is exhibited by SEC filings and statements to analysts as well as the investing public, where these Defendants urged that the product was a rapidly growing product and expected to greatly increase its market presence in the upcoming years.

373. In the 2007 fiscal year alone, according to Medtronic's Second Quarter press release filed with the SEC in November of 2006, "Worldwide Infuse® Bone Graft revenue grew

[172] Medtronic Is Sued Over Bone Product (Dec 3, 2008), (attached hereto as Exhibit 35).
[173] *See* Exhibit 36, "Critique could put bigger drag on Infuse sales" (October 25, 2012).

36 percent, driven by expanded surgeon adoption."[174]

374. In February of 2007, Arthur D. Collins, Jr., Medtronic Chairman of the board responded to Citigroup analyst, Matthew Dodds, about the performance of the BMP/Sponge stating that "Infuse® still grew 15%...**one of the biggest opportunities we have is continuing to expand the indication**." (Emphasis added).[175]

375. During the Goldman Sachs 28th Annual Global Health Care Conference, June 13, 2007, Medtronic's CFO, Gary Ellis stated, "Infuse is…one of our big growth platforms over the next several years."[176]

376. Additionally, MSD's Vice President for Clinical Affairs explained at an Investor and Analyst Meeting on June 20, 2007 that the company was sponsoring several clinical trials to obtain additional FDA approvals for BMP,, including an ongoing Investigational Device Exemption ("IDE") trial examining the its use in Posterolateral Fusion and other studies using it in the cervical spine.

377. FDA approval for these uses was never procured.[177]

378. In 2002, BMP was used in less than 1% of all spinal fusions.

379. By 2006, Infuse® (or its components separately) was used in 25% of all spinal fusions.

380. By 2007, as a result of the Medtronic Defendants' over-aggressive promotion and concealment of dangers associated with use of its components without the Infuse® system, over 40% of PLIF procedures employed components of Infuse® contrary to FDA regulations.

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[174] Medtronic Reports Second Quarter Revenue Growth of 11 Percent (Nov 20, 2006), *available at* http://wwwp.medtronic.com/Newsroom/NewsReleaseDetails.do?itemId=1164113830755&lang=fr_CH (also attached hereto as Exhibit 37).
[175] Exhibit 21, Complaint, as alleged in the shareholder action at Paragraph 192.
[176] *Id.* Exhibit 21 at 207 as alleged in the shareholder action.
[177] *Id.* Exhibit 21 at 208 as alleged in the shareholder action.

381. The majority of growth stemmed from sales of components outside the Infuse® system, which comprised 85-90% of the total annual revenue from Infuse®.[178]

## I. CORPORATE INTEGRITY AGREEMENT BY DOJ IN WHISTLEBLOWER SUITS

382. The Medtronic Defendants also have been named in two prior *qui tam* actions related to Infuse®. These are *United States ex rel. (UNDER SEAL)* v. *Medtronic. Inc., et al.,* Civil Action No. 02-2709 (W. D. Tenn.) (commenced by a former Medtronic employee working as in-house counsel), and *United States ex rel. Poteet* v. *Medtronic, Inc., et al.,* Civil Action No. 03-2979 (W. D. Tenn.) (Collectively the "*qui tam* lawsuits".)

383. The Plaintiffs in both cases alleged violations of the False Claims Act, 31 U.S.C. § 3729, *et seq.* (2012), by paying illegal kickbacks to physicians in order to promote the use of the components and parts of Infuse® outside the approved system and by inducing the submission of false and fraudulent claims to federal health care programs like Medicare and Medicaid.

384. In July 2006, the Medtronic Defendants agreed to pay $40 million[179] to the federal government as part of its agreement to settle two *qui tam* actions under the False Claims Act, 31 U.S.C. §§ 3729-3733 (2012), the Civil Monetary Penalties Law, 42 U.S.C. § 1320a-7a (2012), and the Program Fraud Civil Remedies Act, 31 U.S.C. §§ 3801-12 (2012).[180]

385. In these lawsuits, the United States Department of Justice ("DOJ") contended that between January 1, 1998 and April 30, 2003, Medtronic made payments to physicians and

[178] *See* Emily Jane Woo, *Recombinant Human Bone Morphogenetic Protein 2: Adverse Events Reported to the Manufacture and User Facility Device Experience Database,"* The Spine Journal, 12 (10): 894-899, October 2012 (also attached hereto as Exhibit 38); *see also* John Carreyrou and Tom McGinity, *Medtronic Surgeons Held Back, Study Says*, Wall St. J. June, 29, 2011 (attached hereto as Exhibit 39).

[179] Press Release, Department of Justice (July 18, 2006), *available at* http://www.justice.gov/opa/pr/2006/July/06_civ_445.html (also attached hereto as Exhibit 40).

[180] Medtronic also recently paid $23.5 million to settle allegations regarding Doctor kickbacks related to the sales of pacemakers. *See* Minnesota-Based Medtronic Inc. Pays U.S. $23.5 Million to Settle Claims That Company Paid Kickbacks to Physicians (Dec. 12, 2011), *available at* http://www.justice.gov/opa/pr/2011/December/11-civ-1623.html (also attached hereto as Exhibit 41).

entities in connection with its spinal products, in the form of: (a) payments and other remuneration for physicians' attendance and expenses at medical education events, "think tanks", VIP/Key Opinion Leader events, and meetings at resort locations; (b) access for physicians to Medtronic's Healthcare Economic Services and eBusiness Departments; and, (c) payments made to various physicians and entities, pursuant to consulting, royalties, fellowships, and research agreements associated with Medtronic products.

386. Peter Keisler, Assistant Attorney General for the Department's Civil Division stated in response to the settlement that "*kickbacks to physicians are incompatible with a properly functioning health care system…They corrupt physicians' medical judgment and they cause overutilization and misallocation of vital health care resources.*"[181] (Emphasis added.)

387. Specifically, the *qui tam* lawsuit brought by the former Medtronic counsel disclosed payments in the form of sham seminars and think tanks.

388. Seminars included free travel and lodging for physicians and their families, and were alleged to be without adequate training benefit. The locations ranged from Cancun at the Ritz Carlton, Hawaii, Malaysia and Los Cabos.

389. Additionally, the Medtronic Defendants held all expenses-paid think tanks and study/discussion groups in Alaska, Amelia Island, Arnold Palmer Champions for Children Golf Tournament, New Orleans Mardi Gras (including up to a $25,000 payment to allow physicians to ride on a float and $15,000 spent on Mardi Gras beads), Idaho, Teton Valley and New York, comprising at least 30 think-tanks and groups.[182]

[181] Exhibit 40, Press Release.
[182] *See United States ex rel. (UNDER SEAL) v. Medtronic. Inc., et al.,* Civil Action No. 02-2709 (W. D. Tenn.).

390. The Medtronic Defendants also entertained physicians at strip clubs in Memphis, Tennessee, home to Defendant MSD.[183]

391. These trips were extravagant and these defendants funded visits to strip clubs inappropriately. As revealed hereinafter, the payments disclosed in these actions represented only the tip of the iceberg.

392. Based on its investigation, the DOJ contended that certain of the payments, services, and remuneration mentioned above were improper and resulted in the submission of false or fraudulent claims in violation of the federal Anti-Kickback Statute, 42 U.S.C. § 1320a-7b(b), *et seq.* (2012), which prohibits individuals from offering, soliciting or making any payment or remuneration to induce business reimbursed under a federal or state health care program, and the False Claim Act, 31 U.S.C. § 3729, *et seq.* (2012), which provides penalties for the submission of false claims to the federal government.

393. Under the settlement, the Medtronic Defendants also agreed to enter into a five-year Corporate Integrity Agreement ("CIA") with the U.S. Department of Health and Human Services' Office of Inspector General.[184]

394. The Medtronic Defendants explained in their July 18, 2006 press release that this agreement implemented substantial oversight structures and procedures meant to ensure "***top-level attention to corporate compliance measures***."[185] (Emphasis added.)

395. Among other items, the Corporate Integrity Agreement required the Medtronic Defendants to establish an electronic database to capture and manage all non-sales related

[183] Lawsuit Says Medtronic Gave Doctors Array of Perks, (Sept 25, 2008), *The Wall Street Journal*, (attached hereto as Exhibit 42).
[184] Corporate Integrity Agreement, *available at* http://oig.hhs.gov/fraud/cia/agreements/Medtronic_and_MSD_CIA.pdf (attached hereto as Exhibit 43).
[185] Press Release, Medtronic Resolves Qui Tam Suits (July 18, 2006), *available at* http://www.sec.gov/Archives/edgar/data/64670/000095013406013343/c06802exv99w1.htm (attached hereto as Exhibit 44).

transactions between their corporate spinal subdivision and its physicians or customers, with all transactions subject to an established set of internal controls and review processes, including monitoring by their senior management and Chief Compliance Officer.

396. The settlement also provided for negotiations between these defendants and representatives of the National Association of Medicaid Fraud Control Units for the purposes of distributing certain sums to several states which had been adversely affected by Medtronic's conduct.

**1. Despite The CIA, Medtronic's Off-label Promotion Continues**

397. Medtronic's agent James Kuklo, M.D., a physician who was a former Army Colonel, retired from the military as Chief of Orthopaedic Surgery at Walter Reed Army Medical Center, the nation's premier military research hospital, in December 2006.

398. James Kuklo, M.D. received hundreds of thousands of dollars per year in fees from the Medtronic Defendants following the DOJ settlement.

399. While still on active duty, Col. Kuklo was handsomely compensated by these defendants. From 2001 to 2005, Medtronic's Dr. Kuklo received a total of $42,295 from Medtronic.

400. In 2006, his payments from the Medtronic Defendants went up to $42,627 for the single year.

401. Thereafter, Dr. Kuklo's payments skyrocketed. *The Wall Street Journal* revealed a substantial and dramatic increase in payments from the Medtronic Defendants of $356,242 in 2007, $249,772 in 2008, and $132,453 in the first few months of 2009.[186]

[186] Medtronic Paid the Surgeon Accused Of Falsifying Study Nearly $800,000, (June 18, 2009), (attached hereto as Exhibit 45).

402. The Medtronic Defendants' agent, James Kuklo, M.D., worked closely with these defendants as an active promoter of the "off-label" uses of Infuse®.

403. A U.S. Army investigation uncovered shocking misconduct by the former Army Colonel identifying a falsified study touting the benefits of using the components of Infuse® to treat wounded soldiers in Iraq, despite the fact that this use was considered experimental.

404. The experimental nature of the study was never disclosed to the soldiers who were operated on and in which components of Infuse® were used in this experimental fashion.

405. The U.S. Army never approved the "study".

406. The U.S. Army never received the funds that the Medtronic Defendants paid to fund the "study".

407. Colonel J. Edwin Atwood, an Army physician who led the Army's inquiry, described Kuklo's conduct as "the ultimate tragedy and catastrophe in academic medicine."[187]

408. Dr. Kuklo's "study" purported to compare fusion results of 67 patients who received autogenous bone graft versus 62 that were treated with the BMP/Sponge to treat certain tibial (shin bone) fractures in injured soldiers (including "off-label" uses). The "study" reported that employing the BMP/Sponge resulted in "strikingly" better outcomes than a traditional (autogenous) bone graft.

409. Medtronic's agent James Kuklo, M.D. reported that those receiving autogenous bone grafts had successful fusion in 76% of procedures, while the union rate for the BMP/Sponge group was significantly better at 92%; he claimed that this was a "striking finding."[188]

[187] Discredited Research Study Stuns an Ex-Army Doctor's Colleagues, *The New York Times*, (June 6, 2009), *available at* http://www.nytimes.com/2009/06/06/business/06surgeon.html?pagewanted=all&_r=0 (also attached hereto as Exhibit 46).

[188] Recombinant human bone morphogenetic protein-2 for grade III open segmental tibial fractures from

410. Not only were Medtronic's agent James Kuklo, M.D.'s reported union rates claimed better with the BMP/Sponge than with an autograft, but, according to this falsified study, patients who received the BMP/Sponge also reportedly experienced favorable outcomes in other clinical measures.

411. The study concluded that the primary outcomes measures of union, rate of infection, and reoperation were all improved with rhBMP-2, and that those treated with the BMP/Sponge had a "strikingly lower infection rate (3.2%), which we believe is directly attributable to rhBMP-2."[189]

412. Dr. Kuklo's Medtronic-sponsored study was false, the falsity only uncovered when one of the study's supposed "co-authors," Lt. Col. Romney C. Andersen, was congratulated on its publication by a colleague. After his discovery, Lt. Col. Andersen alerted Army investigators to the false claims.

413. Dr. Kuklo had listed four other Army surgeons as "co-authors" without their knowledge, when these four physicians had neither participated in nor reviewed the article's preparation or submission for publication.

414. The signatures of the four physicians listed as co-authors on the copyright release forms submitted to *The Journal of Bone and Joint Surgery* were forged by Dr. Kuklo.

415. The number of cases cited by Dr. Kuklo in the article differed from the number of cases contained in the Wartime casualty database, with no explanation for the discrepancies in the articles.

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combat injuries in Iraq, *J Bone Joint Surg [Br]*, 2008; 1071, 1068-1072, *available at* http://graphics8.nytimes.com/packages/pdf/business/20090513kuklo-journal-article.pdf (also attached hereto as Exhibit 47).

[189] *Id.* at 1068 and 1071-72.

416. Contrary to Army policy, Dr. Kuklo did not obtain publication review or clearance from Walter Reed prior to submitting the article for publication.

417. The published results of the article suggested a much higher efficacy rate for the BMP/Sponge than was supported by the experience of the purported co-authors.[190]

418. One of the Army's investigators, Col. Norvell V. Coots, cited a higher number of patients and injuries in Dr. Kuklo's study than the hospital could account for. Coots stated "It's like a ghost population that were reported in the article as having been treated that we have no record of ever having existed…this really was all falsified information."[191]

419. After receiving correspondence from Walter Reed dated November 6, 2008 stating that Medtronic's agent James Kuklo, M.D. did not follow Army regulations in submitting the article, that the signatures of the purported co-authors had been forged, and that the article's purported co-authors had questioned the study findings, *The Journal of Bone and Joint Surgery* formally retracted the article and banned Dr. Kuklo from submitting further papers to the Journal.[192]

420. As noted in a May 19, 2009 follow-up article in *The New York Times*, when questioned about its ties to Medtronic's agent James Kuklo, M.D., the Medtronic Defendants repeatedly declined to disclose when it began its financial relationship with the former Army surgeon or the extent of funding it provided.[193]

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[190] Doctor Falsified Study on Injured G.I.'s, Army Says, *The New York Times*, May 13, 2009), *available at* http://www.nytimes.com/2009/05/13/business/13surgeon.html?pagewanted=all&_r=0 (also attached hereto as Exhibit 48.)

[191] *Id.*

[192] Withdrawal of a paper, J. Scott, J Bone Joint Surg. Br. March 2009 91-B:285-286, *available at* http://www.bjj.boneandjoint.org.uk/content/91-B/3/285.extract (also attached hereto as Exhibit 49).

[193] Senator Seeks Data on Doctor Accused by Army of Falsifying a Product Study, (May 18, 2009), *available at* http://www.nytimes.com/2009/05/19/business/19surgeon.html?_r=0 (also attached hereto as Exhibit 50).

421. The funding for the study, which the Army never received, is, to date, unaccounted for. Medtronic's agent James Kuklo, M.D. appeared as a "distinguished guest surgeon" at Medtronic's Spine Division Business Overview Conference Call on September 28, 2006, alongside another Medtronic consultant, Dr. Rick Sasso—who received $150,000 in consulting fees in 2006—as well as Gary L. Ellis, Medtronic Vice President, Corporate Controller and Treasure and Peter Wehrly ("Wehrly"), Medtronic Spinal Division Senior Vice President.

422. During the call, a Merrill Lynch analyst asked about "issues that have come up in the past in terms of potential side effects with using INFUSE in the cervical region," and whether such FDA-unappoved use was a concern for surgeons.

423. Dr. Sasso responded by referring to a "Level 1, controlled randomized study which was published in 2002" which, according to Dr. Sasso, demonstrated that "when you used the appropriate dosage of Infuse®, you did not get problems with esophageal obstruction and problems swallowing."

424. Medtronic's agent James Kuklo, M.D. responded that the question "was well answered as far as appropriate dosage. I think it's really the bottom line."[194]

425. Medtronic's agent James Kuklo, M.D.'s and Dr. Sasso's rendition of the medical literature was not accurate.

426. Drs. Kuklo and Sasso intentionally and with the full knowledge of Medtronic misrepresented the seriousness of the adverse events that Medtronic knew were occurring in the cervical spine – their misrepresentations only hinted at the significant influence of Medtronic's payments had on its consultants' medical judgment.

[194] *Minneapolis Firefighters'* Complaint, Exhibit 21 at 120.

427. Additionally, Senator Grassley discovered that Medtronic's agent James Kuklo, M.D.'s name did not appear on a list of paid consultants for Infuse® provided by the Medtronic Defendants to Senator Grassley that the Senator had requested in a September 30, 2008 letter to the Medtronic Defendants. Senator Grassley disclosed the list the Medtronic Defendants provided – which included 22 physicians who were paid a total of $943,000 from 2005 to 2008 – in a May 18, 2009 letter to these defendants that was published in the *Congressional Record* the following day. According to the May 18, 2009 letter, Senator Grassley was "concerned" that these defendants did not provide their agent James Kuklo, M.D.'s name in response to his inquiry that specifically requested information regarding consultants whose work involves Infuse®, as it was "clear that Dr. Kuklo had some sort of consulting agreement" and was named in *The New York Times* as a consultant for these defendants in regards to Infuse®.[195]

428. By this time, Medtronic's agent James Kuklo, M.D. had given countless presentations promoting the use of the BMP/Sponge component of Infuse® on behalf of the Medtronic Defendants, not to mention his fraudulent "studies".

429. On June 18, 2009, the Medtronic Defendants disclosed to *The Wall Street Journal* that Medtronic's agent James Kuklo, M.D. had received almost $850,000 in payments from these defendants over the past ten (10) years, the majority of which – nearly $800,000 – were made in the preceding three (3) years when Dr. Kuklo was shopping his study to medical journals.

430. The Medtronic Defendants paid their agent James Kuklo, M.D. $356,242 in 2007, the year their agent James Kuklo, M.D. sought publication of the study in two medical journals.

431. The Medtronic Defendants paid Dr. Kuklo $249,772 in 2008, the year the study

[195] Letter, Letter to Medtronic, Inc. (May 18, 2009), *available at* http://www.gpo.gov/fdsys/pkg/CREC-2009-05-19/html/CREC-2009-05-19-pt1-PgS5609-2.htm (also attached hereto as Exhibit 51).

was published.[196]

432. The Medtronic Defendants made both of these payments after it announced its settlement with the DOJ in July of 2006.

433. The Medtronic Defendants placed their KOL James Kuklo, M.D. on "inactive status" only ***after*** reports that he falsified the study's data were published in *The New York Times.*

### J. $85 MILLION TO SETTLE SHAREHOLDER SUIT RE: OFF-LABEL PROMOTION

434. *Minneapolis Firefighters' Relief Association v Medtronic, INC, et.al*, 08-06324, U.S. District Court, District of Minnesota (Minneapolis)[197] was brought on behalf of institutional shareholders and arose from allegations of the Medtronic Defendants' materially false, misleading, and incomplete public statements concerning Infuse®, notably including over-aggressive promotion of its components outside the FDA approved system.[198]

435. Judge Magnuson in the United States District Court for the District of Minnesota described the shareholder action, in part, in his Memorandum and Order on December 12, 2011 as follows:

> a. "Infuse is a surgically-implanted medical device containing a genetically engineered protein designed to stimulate bone growth." (Am. Compl. (Docket No. 68) ¶ 1.) Medtronic received approval from the Food and Drug Administration ("FDA") for certain specific uses on Infuse®: treatment of degenerative discs in the lower lumbar region of the spine, fractures of the tibia, and certain facial/oral surgeries." *See Minneapolis Firefighters' Relief Ass'n v. Medtronic, Inc.*, 278 F.R.D. 454, 456 (D. Minn. 2011)
>
> b. Plaintiffs' claims arise from what they characterize as Medtronic's intentional promotion of off-label use for Infuse®. A physician's use of a device in a manner not specifically approved by the FDA is not illegal. It is

[196] Exhibit 45.
[197] *See* Exhibit 21, *Minneapolis Firefighters'* Complaint.
[198] Jonathan Stempel, *Medtronic to pay $85 million to settle Infuse lawsuit*, Reuters, (March 31, 2012), *available at* http://206.132.6.104/article/2012/03/30/us-medtronic-settlement-idINBRE82T1A920120330 (also attached hereto as Exhibit 52).

illegal, however, for a manufacturer to promote device's off-label use. Plaintiffs contend that Medtronic engaged in such promotion, and that eventually more than 85% of Infuse® sales involved off-label use. (*Id*. ¶ 3)…[t]he Infuse product generated approximately $800 million annually or 6% of Medtronic's total corporate revenue. (*Id*. ¶ 40.) In the summer of 2008, the FDA issued a warning about a particular off-label use of Infuse® and several months later, Medtronic disclosed that it was the target of an investigation by the Department of Justice ("DOJ") regarding off-label use of Infuse®." *Id.*

c. "Specifically, Plaintiffs allege that Medtronic both implicitly and explicitly encouraged its sales force to promote the off-label use of Infuse®. Plaintiffs rely on the testimony of 15 confidential witnesses to support this allegation." *Id.*

d. "According to the Amended Complaint, the information provided by the confidential witnesses either established or implies that Medtronic actively promoted off-label uses for Infuse® by, among other things**, hosting physician meetings at which a Medtronic-paid consulting physician would give a presentation on off-label uses** (Am. Compl. ¶ 93), **instructing its sales force in the off-label use of Infuse®** *(Id.* ¶ 94), **giving physicians literature about off-label uses for Infuse®** *(Id.* ¶ 96) **or directing physicians to other surgeons who used Infuse® for off-label procedures** (*Id*. ¶ 102), **and advising physicians regarding the appropriated dosage of Infuse® for off-label uses** (*Id*. ¶ 105). Plaintiffs also claim that Medtronic set high sales targets for Infuse and knew or should have known that such high targets could be reached only through illegal promotion of off-label uses of Infuse." (e.g., *Id*. ¶ 107).[199] *Id.* (Emphasis added).

### 1. Systematic "Off-Label" Promotion through Medtronic's Agents

436. As noted by Judge Magnuson, according to former employees in the shareholder action against the Medtronic Defendants, these defendants engaged in systematic "off-label" promotion.

437. Some of the techniques alleged in the shareholder action used by these defendants include: sponsoring "off-label" presentations by "opinion leaders;" providing sales representatives specific, step-by-step instructions regarding the dosage and techniques of "off-

[199] Memorandum and Order at 2-3, *Minneapolis Firefighters' Relief Association v Medtronic, INC., et.al,* 08-06324, U.S. District Court, District of Minnesota (also attached hereto as Exhibit 53).

label" use of Infuse®, including how to roll the ACS (collagen sponge) like a "burrito" to optimize its fit in the spine (without the approved cage); directing physicians to other doctors who had alleged "success" using Infuse® "off-label"; sending Medtronic representatives, who were not medically-trained, into the operating room during surgical procedures involving Infuse®; and finally, setting sales quotas that would not have been met absent "off-label" sales.[200]

438. These former employees worked for and represented the Medtronic Defendants at various levels of management and sales at private meetings, conferences, and hospitals with physicians across the United States, demonstrating that these practices were widespread throughout the defendants, rather than isolated to particular areas.

a. **Sponsoring off-label physician meetings and corporate visits**

439. The Medtronic Defendants promoted the "off-label" use of Infuse® in several ways, often by sponsoring meetings targeted toward physicians.

440. One confidential witness was employed by the Medtronic Defendants as a territory sales manager in the southeastern United States from 2002 through 2005.

441. This confidential witness disclosed that these sponsored events included meetings for local physicians to attend presentations on the "off-label" use of Infuse® given by Medtronic-paid surgeons.

442. These meetings, as well as corporate visits for physicians to receive "off-label" training by guest surgeons, included those from the Norton Leatherman Spine Center in Louisville, Kentucky, a clinic that had agreed to split royalties with these defendants in exchange for helping to develop spinal implants.[201]

[200] *Id.*
[201] *See* Exhibit 21 at Paragraph 93.

443. The Medtronic Defendants consistently hired and slotted surgeons at its national sales meetings to educate Medtronic sales representatives on the "off-label" uses of Infuse®, according to Kirk Riley, a Spinal sales representative who promoted Infuse® sales in the Northeast United States from 2002 until 2006.[202]

444. The Medtronic Defendants actively recruited doctor-experts to engage in peer-to-peer conversations with other doctors regarding Infuse®, according to Matt Tosch, another sales representative who promoted Infuse® sales in the Northeast United States in 2002 and 2003.[203]

**b. Instructing its sales representatives to sell off-label dosages**

445. The Medtronic defendants held regional and national sales team meetings during which sales representatives received specific instructions on how to administer Infuse® for various "off-label" uses, in order to convey these specifics to the doctors using Infuse® off-label, according to the confidential witness employed by these defendants as a territory sales manager. These sales representatives were specifically instructed not to document any of the information they passed on to the doctors, and to limit communications to verbal form.[204]

446. Additionally, Chris Powell, a Biologics sales representative who promoted Infuse® sales in the Mid-Atlantic United States in 2005, confirmed that Medtronic showed its sales staff how to use Infuse® "off-label".[205]

**c. Citing "studies" to "educate" surgeons in off-label surgical techniques**

447. The Medtronic Defendants' response to physician inquiries on the "off-label" uses for Infuse® was to provide data from published literature and other information reinforcing the "off-label" use of Infuse®, according to Matthew Bine.

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[202] *See id.* at Paragraph 100; *see also* Exhibit 53, Memorandum and Order identifying the names of confidential witnesses.
[203] *See* Exhibit 21 at Paragraph 107; *see also* Exhibit 53.
[204] *See* Exhibit 21 at Paragraph 94.
[205] Exhibit 53 at 9.

448. Mr. Bine was a product manager for Medtronic's Biologics Marketing, who promoted Infuse® sales from 2005 to 2008.[206]

449. The Medtronic Defendants did not seek the prior approval of the FDA, nor comply with the Safe Harbor provisions before distributing the promotional materials regarding the "off-label" use of Infuse®. Nor did they disclose any part Medtronic employees played in crafting the published articles. Nor did they disclose the enormous sums paid to the "scientists" conducting the "studies" contained in the published articles they were citing.

**d. Referring surgeons to "off-label" users of Infuse® for clinical advice**

450. According to Scott Baumer and Mark Marchan, if a spine surgeon inquired about the "off-label" use of Infuse®, employees of the Medtronic Defendants would suggest that the doctor making the inquiry talk to other off-label users.

451. Mr. Baumer was a spinal sales representative who promoted Infuse® sales in Northwestern United States from 1998 to 2003.[207] Mr. Marchan was a clinical data director.[208]

452. Additionally, if a doctor inquired into how to use Infuse® "off-label", a Medtronic sales representative would direct the doctor to other surgeons who had used the product "off-label", and the sales representative would offer to demonstrate or explain the technique, according to Chris Powell, a Biologics sales representative.[209]

**e. "Informing" surgeons on off-label dosages in the cervical spine**

453. As early as 2006, doctors have reported adverse events associated with the "off-label" use of Infuse® in the cervical spine. These events included swelling, dysphagia and

[206] Exhibit 21 at Paragraph 96; *see also* Exhibit 53.
[207] *See* Exhibit 21 at Paragraph 103; *see also* Exhibit 53.
[208] *See* Exhibit 21 at Paragraph 102; *see also* Exhibit 53.
[209] *See* Exhibit 21 at Paragraph 99; *see also* Exhibit 53.

dysphonia, according to Matthew Bine, the product manager for Medtronic's Biologics Marketing.

454. The Medtronic Defendants did not address the issue properly and according to FDA Regulations, by not informing the surgeons that the use of the BMP/Sponge in the cervical spine was "off-label" and not proven safe or effective. Instead, these Defendants assured doctors that smaller doses of rhBMP-2 used in the cervical spine would alleviate the incidence of adverse events. Bine reported that "our goal was to tell surgeons, don't put 2.8 on; put 1.4 or 0.7 [in "off-label" cervical applications]." Furthermore, Bine noted that Infuse® kits containing the BMP/Sponge component became available in these smaller sizes, even though the FDA-approved uses remain the same.[210]

455. This is specific (and indisputable) evidence of the objective intent of the Medtronic Defendants to provide packaging of its product accommodating off-label uses, such as in the cervical spine.

456. The Medtronic Defendants instructed its sales representatives to advise doctors to use roughly half the indicated dosage of rhBMP-2 (or 1.4 cc) in cervical applications, according to Kirk Riley, another spinal sales representative. Riley also confirmed that the Medtronic Defendants were aware of swelling in the neck caused by cervical applications of BMP, but that in response, Medtronic merely recommended that each surgeon prescribe steroids to treat these symptoms.[211]

457. Mr. Riley further reported that when surgeons first began to use BMP in cervical fusion surgeries, they were not aware of the potential adverse consequences of using an entire sponge (or full rhBMP-2 dosage) in the cervical spine. After Medtronic's national sales

[210] *See* Exhibit 21 at Paragraph 97; *see also* Exhibit 53.
[211] *See* Exhibit 21 at Paragraph 100; *see also* Exhibit 53.

meetings, however, the instructions on how to use BMP in the cervical spine--even though the product was only FDA-approved for lumbar anterior fusion--became so widespread throughout the medical community that information on how to use "off-label" Infuse® was readily available.[212]

458. One of the confidential witnesses disclosed that when adverse reactions were reported in conjunction with the cervical application of BMP in 2006, the Medtronic Defendants organized a conference call with its sales representatives to instruct them that surgeons should not be using the "whole sponge" (or full rhBMP-2 dosage) in cervical fusion surgery. These defendants disregarded the fact that cervical surgeries with BMP were "off-label", not FDA-approved as it was not an "intended use" of Infuse® in the PMA and therefore it was a violation of federal law and the PMA for them to provide anyone with such instructions or information.[213] This was also confirmed by Mark Marchan, a clinical data director who was employed by Medtronic from 2000 to 2007.[214]

**f. Showing surgeons how to roll the Infuse® sponge "like a burrito"**

459. The Medtronic Defendants' sales representative would show surgeons how to perform a specific procedure by rolling up the BMP/Sponge material "like a burrito" to place into the lateral spine, according to Chris Powell, a Biologics sales representative.

460. Victor Harmon was a Medtronic sales associate from 2000 to 2004 in the Southwestern region of the United States.

461. He recalled a meeting with Medtronic's regional management discussing how to "get around" restrictions on "off-label" promotion where "[Medtronic's regional management]

[212] *See* Exhibit 21 at Paragraph 100; *see also* Exhibit 53.
[213] *See* Exhibit 21 at Paragraph 102; *see also* Exhibit 53.
[214] *See* Exhibit 21 at Paragraph 102; *see also* Exhibit 53.

talked about rolling [it] into almost a little taco in the lateral gutters."[215]

**g. Infuse® sales (over 85-90%) were from "off-label" uses**

462. According to Sean Hirschkorn, the vast majority of Infuse® surgeries were "off-label" applications.

463. Mr. Hirschkorn was a sales representative who promoted Infuse® sales in Southwestern United States and who was employed by the Medtronic Defendants from 2004 through 2008. The reason that the vast majority of Infuse® surgeries were "off-label" applications was because very few surgeons used the LT-CAGE or Anterior Lumbar Interbody Fusion ("ALIF") procedure, which would have constituted FDA-approved use of Infuse®. According to Hirschkorn, the Posterior Lumbar Interbody Fusion ("PLIF") and Transforaminal Lumbar Interbody Fusion ("TLIF") "off-label" procedures were far more common surgeries than an ALIF surgery in the lumbar region.[216]

464. Chris Eddy, a regional sales manager in Northwestern United States from 2002 to 2004, also reported that the vast majority of Infuse® sales were for "off-label" uses, citing the high volume of sales coupled with very low numbers of ALIF procedures (the only FDA-approved spinal procedure) actually being performed.[217]

465. Victor Harmon, a sales associate, corroborated these reports by disclosing that the vast majority of Infuse® procedures were in fact "off-label" and that the product was "tremendous" with regard to Medtronic's overall growth.[218]

**h. Packaging the LT-Cage separately, knowing the rhBMP-2 component out-sold its Cage**

466. Sales of the Infuse® rhBMP-2 component far outsold sales of the LT-CAGE,

[215] *See* Exhibit 21 at Paragraph 104; *see also* Exhibit 53.
[216] *See* Exhibit 21 at Paragraph 105; *see also* Exhibit 53.
[217] *See* Exhibit 21 at Paragraph 106; *see also* Exhibit 53.
[218] *See* Exhibit 21 at Paragraph 104; *see also* Exhibit 53.

according to sales representative Matt Tosch.

467. Tosch reported that the Medtronic Defendants pressured its sales representatives to reach high sales targets, which those defendants increased every year,[219] thus contributing to the discrepancy of "on-label" sales of these components together, versus "off-label" sales, separately.

468. The Medtronic Defendants packaged and sold the two components of Infuse® separately, even though both parts were needed for each spinal surgery, as required by the FDA.

469. According to a product manager for Medtronic's Biologics Marketing, Matthew Bine, by the time he left Medtronic, Infuse® sales for "off-label" use accounted for the vast majority of total sales.

470. According to Bine, sales of the rhBMP-2 component of Infuse® greatly outpaced sales of the LT-CAGE, which were packaged and sold separately, although these components must be used together according the FDA-approved label.[220]

471. Furthermore, Charles Koenig, a spinal financial analyst, employed by the Medtronic Defendants from 2002 through 2007, stated that it was his "impression that Infuse® was used in off-label procedures."[221]

**i. Quotas for Infuse® sales could not be achieved by "on-label" alone**

472. The Medtronic Defendants set sales quotas for Infuse® that were much higher than what could possibly be achieved through FDA-approved sales.

473. "[T]here was no way" that Medtronic executives could have expected the sales quotas to be met without "off-label" sales, according to the confidential witness who served as territory sales manager for southeastern United States.[222]

[219] *See* Exhibit 21 at Paragraph 107; *see also* Exhibit 53.
[220] *See* Exhibit 21 at Paragraph 98; *see also* Exhibit 53.
[221] *See* Exhibit 21 at Paragraph 108; *see also* Exhibit 53.

474. According to Chris Powell, the sales related to "off-label" use of Infuse® were necessary to satisfy sales quotas and the *minimum* 20% annual sales growth required by management of the Medtronic Defendants.

475. Chris Powell was employed by Medtronic as a Biologics sales representative.[223]

476. The Medtronic Defendants' sales representatives knew that they could not reach sales targets without "off-label" sales, according to Chris Eddy, a spinal regional sales manager.[224]

477. The Medtronic Defendants set very high sales targets of 15-20% growth per year, and Medtronic's Spine (and mainly) Biologics division were considered "one of the big growth engines of Medtronic," according to Matthew Bine, a product manager for Medtronic's Biologics Marketing. Bine further reported that 95% of Infuse® revenues related to spinal usage (cervical and lumbar), with only 5% allocated from trauma and oral maxillofacial applications.[225]

478. Taken together, the Medtronic Defendants profited extremely, exponentially, and directly from "off-label" Infuse® sales with each passing year.

**j. Providing step-by-step "off-label" surgical instructions**

479. Medtronic's sales representatives participated in surgeries by providing surgeons with step-by-step instructions on how to use Infuse®, even when the product was used "off-label", according to a confidential witness who was employed by Medtronic as an associate sales representative in the South, Southwest, and Midwest. The witness further disclosed that "off-label" use of Infuse® was far more common than "on-label" use, which was "few and far

[222] *See* Exhibit 21 at Paragraph 95; *see also* Exhibit 53.
[223] *See* Exhibit 21 at Paragraph 99; *see also* Exhibit 53.
[224] Exhibit 53 at 16.
[225] Exhibit 21 at Paragraph 98; *see also* Exhibit 53.

between."[226]

480. It was common practice for the Medtronic Defendants' sales representatives to be present in the operating room for surgeries using BMP, and sales representatives were in fact encouraged by the Medtronic Defendants to attend such surgeries, according to the associate sales representative.[227]

481. Medtronic expected its sales representatives to be present in the operating room during procedures with BMP "to assist and direct and give advice when asked," according to the territory sales manager for Southeastern United States.[228] Matthew Bine, a product manager for Medtronic's Biologics Marketing division, corroborated Medtronic's policy of sending sales representatives into operating rooms.[229]

482. Medtronic sales representatives were often present in the operating room to demonstrate to the doctor how to assemble the sponge, or to explain other procedures and assist with any issues that may arise, according to Chris Powell, a Biologics sales representative.[230] This was also confirmed by both Mark Marchan, a clinical data director,[231] as well as Kirk Riley, a Spinal sales representative.[232]

**k. Medtronic agents training other surgeons "off-label"**

483. Medtronic agents, Lawrence "Larry" G. Lenke, M.D. and Keith H. Bridwell, M.D., two surgeons from Washington University in St. Louis, where Dr. Kuklo worked as an associate professor, similarly acted as "Opinion Leaders" or "guest surgeons" during "corporate visits" in which Medtronic would invite unsuspecting targeted surgeons to attend training

[226] *See* Exhibit 21 at Paragraph 101.
[227] *See* Exhibit 21 at Paragraph 101.
[228] *See* Exhibit 21 at Paragraph 95; *see also* Exhibit 53.
[229] *See* Exhibit 21 at Paragraph 97; *see also* Exhibit 53.
[230] *See* Exhibit 21 at Paragraph 99; *see also* Exhibit 53.
[231] Exhibit 53 at 12.
[232] *See* Exhibit 53; *see also* Exhibit 21 at Paragraph 99.

sessions in Memphis, Tennessee.

484. While in Memphis, the visiting surgeons met with Medtronic corporate officers, product managers, and guest surgeons, such as Lawrence "Larry" G. Lenke, M.D. and Keith H. Bridwell, M.D. The visiting surgeons also received "hands-on training" on Infuse®, including instruction in cadaver labs. The visiting surgeons "would bring up the use of Infuse® and ask how to use it, and [the guest surgeons] would show them how to do it." Medtronic chose which surgeons to invite to these corporate visits based, in part, upon the volume of Infuse® procedures they performed.[233]

**2. Confidential Witnesses Prove "Off-Label" Promotion**

485. Judge Magnuson found that following statements were in fact made by former Medtronic employees:

a. "*Medtronic did provide information to doctors about appropriate doses of Infuse® for off-label use,*" stated by Chris Powell ;[234]

b. "*Medtronic showed its sales staff how to use Infuse® off-label so that they could support the safe use of the product,*" stated by Chris Powell;"[235]

c. *Medtronic instructed its sales representatives to refer doctors to the Office of Medical Affairs with questions about dosages in off-label uses, but that if a physician had a question about dosage in the operating room, the sales representative could answer the question to "support patient safety,"* stated by Kirk Riley;[236]

d. *"[i]t is true that I attended surgical procedures involving Infuse® in the operating room, and if asked questions by the doctors concerning the procedure, I would answer his questions to the best of my ability as part of my role to support patient safety,"* stated by Kirk Riley;[237]

e. In reference to a doctor's inquiry about "off-label" uses with information about other surgeons using the product "off-label", Scott Baumer disclosed,

[233] Exhibit 21 at Paragraph 140.
[234] Exhibit 53 at 8.
[235] *Id. at* 9.
[236] *Id. at* 10.
[237] *Id. at* 11.

*"that when faced with such questions about off-label use, his 'practice was simply to suggest that the doctor making the inquiry talk directly to the other doctor'";*[238]

f. Chris Eddy disclosed, in relation to directing inquiring doctors to others who were using Infuse® "off-label," *"he and sales representatives he supervised would direct physicians to Medtronic's Office of Medical Affairs;"*[239]

g. Charles Koenig states his *"impression was that [Infuse] was used in off-label procedures;"*[240] and,

h. Derek Crim, who worked for Medtronic in 2008 stated that Medtronic set sales quotas that were *"very, very, very aggressive."*[241]

486. On February 1, 2012, Judge Magnuson upheld Chief Magistrate Judge Boylan's holding that Confidential Witness 2 had waived any Fifth Amendment privileges in the documents being sought.[242]

487. Thereafter, on March 30, 2012, Medtronic agreed to pay $85 million to settle the shareholder lawsuit pertaining to alleged illegal "off-label" over-promotion of Infuse®.[243]

### K. "OFF-LABEL" USE IN THE LUMBAR SPINE IS NEITHER SAFE NOR EFFECTIVE

488. Susan Levine, a Vice President at Hayes, Inc., a company which evaluates medical technologies for insurers, expressed concern over the Medtronic Defendants' handling of Infuse®.

489. Upon her review of the research conducted on Infuse®, Ms. Levine stated that it is "distressing to see something like this used in a potentially harmful way and without adequate evidence."[244]

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[238] *Id. at* 13.
[239] *Id. at* 10.
[240] *Id.* at 18.
[241] *Id.* at 20.
[242] Order at 1-2, Minneapolis Firefighters' Relief Association v Medtronic, INC., et.al, 08-06324, U.S. District Court, District of Minnesota (also attached hereto as Exhibit 53).
[243] Medtronic to settle suit for $85 million, (Mar 30, 2012), *available at* http://www.startribune.com/business/145214355.html (also attached hereto as Exhibit 54).
[244] Medtronic Product Linked to Surgery Problems, (Sept 4, 2008), (attached hereto as Exhibit 55).

490. Prior Medtronic-sponsored studies demonstrated that the use of Infuse® outside of the FDA approved system presented serious adverse events and risks to patient safety.

491. Dr. David Malone, a surgeon from Oklahoma involved with an earlier study (led by Medtronic's agent Regis Haid, M.D.) had first-hand experience with the adverse effects of such use.

492. Dr. Malone had two patients who suffered from significant posterior bony over-growth impinging on their nerve roots as a result of such use and who subsequently required revision surgeries.

493. Dr. Malone noted these adverse events by stating, "BMP may lead to excessive bone growth and may cause significant neural impingement if placed in the posterior lumbar interbody space."[245]

494. The study that Dr. Malone was involved in was abruptly discontinued due to bony overgrowth at the annulotomy site.

495. A computed tomography ("CT") scan evaluation detected new bone growth in the spinal canal or neuroforamina in 24 of 32 rhBMP-2 patients.[246]

496. Subsequent studies have indeed shown that 25% to 50% of PLIF surgeries are riddled with complications and adverse events.[247]

497. Medtronic was well aware of these dangers.

498. In a May 15, 2006 article in *The Spine Journal* notes, "rhBMP-2 may stimulate bone growth in areas in which bone is not desired, especially as the material 'leaks' into such spaces…Although this phenomenon has not been thoroughly studied, it implies that the release

[245] Exhibit 22 at 29. *See also,* Eugene J. Carragee, Alexander J. Ghanayem, Bradley K. Weiner, *A challenge to integrity in spine publications: years of living dangerously with the promotion of bone growth factors,* 11 Spine J. 481, 463-468 (2011) (also attached hereto as Exhibit 56).
[246] *Id.* at 480.
[247] *Id.* at 487.

of rhBMP-2 into the soft tissues stimulates a rapid, potentially life-threatening, inflammatory reaction."[248]

499. Thousands of patients have been reportedly harmed by using the BMP component of Infuse® outside the FDA approved system.

500. At least 3,585 reports of adverse events involving the BMP component of Infuse® have been made to the FDA as of March 2013,[249] and approximately 85-90% of all surgeries using Infuse® us its components outside the FDA approved system.[250]

501. It is well known by the FDA that adverse events involving medical devices are underreported. "A 1986 General Accounting Office (GAO) study showed that less than one percent of device problems occurring in hospitals are reported to FDA, and the more serious the problem with a device, the less likely it was to be reported. A GAO follow-up study in 1989 concluded that despite full implementation of the Medical Device Reporting (MDR) regulation, serious shortcomings still existed."[251]

### L. USE OF KEY OPINION LEADERS (KOLS) FOR PROMOTION

502. Medical device companies look for surgeons who are known as "Key Opinion Leaders" ("KOLs") and who will use a high volume of their devices.

503. KOLs are physicians whose opinions on medical procedures and medical devices are held in high regard.

504. If these influential physicians are willing to promote the use of a certain device, it

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[248] Patel W, et al., *Controlling Bone Morphogenetic Protein Diffusion and Bone Morphogenetic Protein Stimulated Bone Growth Using Fibrin Glue*, Spine Journal Vol. 31, 1201-1206 (2006) (also attached hereto as Exhibit 57).

[249] MAUDE – Manufacturer and User Facility Device Experience, *available at* http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.CFM.

[250] Exhibit 27, Senate Report at 3.

[251] http://www.fda.gov/medicaldevices/safety/reportaproblem/default.htm (also attached hereto as Exhibit 58).

is thought that other surgeons will follow suit, even if the promoted use is "off-label" and not FDA-approved.

505. The Medtronic Defendants cultivated financial relationships with KOLs, paying them handsomely (in the case of Infuse®, these figures can exceed $30 million, per physician) for consulting fees, disguised royalties, travel expenses, seminars, and other perks, in order to encourage and reward these physicians for promoting the use of a particular medical device like Infuse®.

506. The Medtronic Defendants not only engaged in such activities with respect to Infuse® in general; it improperly paid doctors specifically to promote, both directly and indirectly, the "off-label" use of Infuse® in spinal fusion surgeries.

### M. MARKETING WITH WEBSITES, WITHOUT FDA APPROVAL

#### 1. Misrepresenting BMP on Medtronic's Websites

507. The Medtronic Defendants misrepresented the efficacy of BMP directly to physicians through its corporate sponsored websites.

508. Medtronic misrepresented the efficacy of BMP directly to potential patients through its corporate sponsored websites.

509. The Medtronic Defendants, through their website, www.Medtronic.com, falsely claims that "[b]one formation remote from the site of the implantation was not seen in the clinical trials."[252] As of the date of the filing of this complaint, Medtronic holds this information out to the public.

510. The Medtronic Defendants are fully aware of multiple studies which have confirmed uncontrolled ectopic bone growth following a fusion using BMP.

[252] Questions and Answers – Infuse Bone Graft and LT Cage Device, *available at* http://www.medtronic.com/patients/lumbar-degenerative-disc-disease/surgery/questions-and-answers/index.htm (also attached hereto as Exhibit 59).

511. The Medtronic Defendants' website exaggerates the side effects of Infuse®/BMP alternatives.

512. The Medtronic Defendants mislead viewers through the bolded section "**I have heard people talk about hip pain after harvesting lasting up to 2 years or longer. Is that true?**"[253]

513. The Medtronic Defendants know or should know that it is a violation of federal law and the Infuse® PMA to make representations about the use of an approved Class III medical device that goes beyond the "intended uses" set forth in the premarket application as well as the approved labeling.

514. A recent United States Senate Report, released October, 2012 uncovered that fears relating to "donor site" hip pain were manufactured by one of Medtronic's Vice Presidents, who is quoted as saying "plant the seed of doubt" in regards to pain from autograft bone harvesting.[254]

515. The Medtronic Defendants warrant a 94.5% fusion rate with Infuse® compared to autograft's 88.7% on the company sponsored website www.infusebonegraft.com.[255]

516. The purported success rates are derived from two studies provided on the website. The Medtronic Defendants paid five of the seven authoring physicians of these articles collectively $76,603,827 in various forms of compensation.[256] Medtronic did not adequately disclose their financial relationship with these physicians, and it failed to provide accurate and unbiased information to physicians and patients on its corporate sponsored website.

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[253] *Id.*
[254] Exhibit 13 at 2.
[255] Clinical Research – Infuse® Bone Graft LT-Cage® Device, *available at* https://www.infusebonegraft.com/clinical_research (also attached hereto as Exhibit 60).
[256] Dr. Burkus $6,380,336, Dr. Gornet $3,985,776, Dr. Dickman $3,272,942, Dr. Zdeblick $34,168,739, and Dr. Boden, $28,796,034; Exhibit 27 at 5.

### 2. Promotion on Back.com, in Violation of FDA Regulation

517. Following FDA Approval of Infuse®, the Medtronic Defendants published a website providing back pain resources, including surgical and non-surgical treatment options. The website highlights the fact that its information is "brought to you by Medtronic."[257]

518. Surgical options described on the website include Spinal Fusion, ALIF, DLIF, PLIF, and TLIF.[258]

519. The Medtronic Defendants posted a section on June 27, 2002 entitled "Surgery from the Front or Back: Is There a Difference?"

520. The author, Dr. Thomas Schuler, discussed the benefits and complications related to ALIF (approved use of Infuse®) and PLIF (an FDA unappoved procedure when used with the BMP in Infuse®).[259]

521. Dr. Schuler first discussed the complications related to a PLIF surgery conducted without the advantages afforded by the BMP in Infuse®. He shares that PLIFs frequently require an autograft, which is bone generally removed from the pelvis or iliac crest of the patient using either chisels or different awls and further states:

a. *[t]he reason for taking the autograft is that it is very effective and is the gold standard for use in the fusion surgery that we have had to date. The problem with the removal of this bone is that it can be very painful. In fact, around 25% of patients who have had this bone graft procedure have some sort of chronic pain associated with the graft site after surgery*.[260] (Emphasis added.)

b. Dr. Schuler then describes the benefits of the BMP in Infuse®, asserting the following:

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[257] http://www.back.com (also attached hereto as Exhibit 61).
[258] Back,com, Treatment Options, Jan. 15, 2002, *available at* http://www.back.com/treatment.html (also attached hereto as Exhibit 62).
[259] Dr. Thomas Shuler, *Surgery from the Front or Back: Is There a Difference*, Back.com, June 27, 2002, *available at* http://www.back.com/article-schuler.html?infusebox=true (also attached hereto as Exhibit 63).
[260] *Id.*

> ***the beauty of this substance is that it will allow us to obtain a solid fusion without any of the complications of harvesting bone graft.*** *In essence, surgeons get the same or better results without the problems. For patients who are petrified of pain and bone grafts, this is wonderful news.*[261] (Emphasis added.)

522. In February of 2009, the Medtronic Defendants published an entire section on this website dedicated to the benefits of PLIF, a procedure that is FDA unapproved if done with the BMP in Infuse®.[262]

523. The Medtronic Defendants wrote that "PLIF is a type of spine surgery that can be performed in a minimally invasive way" and "involves approaching the spine from the back (posterior) of the body to place ***bone graft material*** between two adjacent vertebrae (interbody) to promote bone growth that joins together, or "fuses" the two structures (fusion)."[263] (Emphasis added.)

524. The Medtronic Defendants further asserted that this "minimally invasive procedure allows many patients to be discharged the day after surgery" and that "[m]any patients will notice immediate improvement of some or all of their symptoms."[264]

525. In 2004, Medtronic sponsored a study heralding the benefits of a PLIF surgery performed with Infuse®.[265]

526. As of 2007, BMP was used in at least 40% of PLIF surgeries.[266]

527. In 2010, The Medtronic Defendants published a section on their sponsored website that was dedicated to Direct Lateral Interbody Fusion (DLIF), a FDA unappoved procedure when used with the BMP in Infuse®. Similar to PLIF, the article claimed that "DLIF

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[261] *Id.*
[262] *Posterior Lumbar Interbody Fusion (PLIF)*, Back.com, Feb. 19, 2008, *available at* http://www.back.com/treatment-surgical-posterior.html (also attached hereto as Exhibit 64).
[263] *Id.*
[264] *Id.*
[265] *Id.*
[266] Eugene J. Carragee, Eric L. Hurwitz & Bradley K. Weiner, *A critical review of recombinant human bone morphogenetic protein-2 trials in spinal surgery: emerging safety concerns and lessons learned*, 11 Spine J. 471, 480 (2011) (also attached hereto as Exhibit 65).

is one of several minimally invasive spine procedures available today and is an approach to interbody fusion [that] offers surgeons and their patients a less invasive option for spine surgery."[267]

528. The website also provides the corroborative insight of Dr. Richard Hynes, who declares that "DLIF is another 'next-generation' step in the process" of spinal fusion.

529. Dr. Hynes enthusiastically recommends that a patient considering DLIF or any other spinal fusion should "[d]o your homework!" and "talk to your doctor, go to reputable websites such as Back.com to learn all about the procedure as well as any other options that are available."[268]

530. The Medtronic Defendants posted a section on its website dedicated to Transforaminal Lumbar Interbody Fusion (TLIF), stating "TLIF is a procedure that can be performed using minimally invasive spine surgery."[269]

531. The sections on the website related to PLIF, DLIF and TLIF do not refer to the use of Iliac Crest Bone Graft ("ICBG") harvested from the patient, but rather refers to "***bone graft material***" that can facilitate "**minimally invasive**" spinal surgery.

532. According to Medtronic-sponsored studies on PLIF and the previously posted article published on Back.com, a surgery using ICBG is anything but "minimally invasive."

533. According to Medtronic Defendants, ICBG is surgery accompanied by a litany of complications related to harvesting the bone graft from the patient's hip.

534. The Medtronic Defendants' omission of the need for bone harvesting and the existence of adverse effects related to PLIF, DLIF and TLIF on its sponsored website Back.com

[267] *Direct Lateral Interbody Fusion – A Minimally Invasive Approach to Spinal Stabilization* Back.com, Feb. 4, 2010, *available at* http://www.back.com/treatment-surgical-direct.html (also attached hereto as Exhibit 66).
[268] *Id.*
[269] *Id.*

is thus an "off-label" promotion for Infuse®, since the procedures can only be accomplished as advertised through the "off-label" use of Infuse®.

535. The Medtronic Defendants have since used Back.com to actively promote the use of PLIF, DLIF, and TLIF as a surgical option while sponsoring studies that exaggerated the complications associated with non-Infuse® PLIFs, violating federal law and the PMA restrictions.

536. The Medtronic Defendants' misleading statements, along with repudiated Medtronic-sponsored studies regarding the "off-label" use of Infuse®, evidences these defendants' over-promotion of the use of Infuse® in "off-label" spinal fusion, made with full knowledge that such statements are highly misleading.

**3. Promotion on Necksurgery.com Violates FDA Regulations**

537. The Medtronic Defendants published Necksurgery.com touting the website as "[t]he online resource for questions about neck pain, spinal health and treatment options." This site conspicuously states that it is "brought to you by Medtronic."[270]

538. Necksurgery.com lists several surgical options for the neck, which include Anterior Cervical Discectomy with Fusion (ACDF), an "off-label" surgery when performed with Infuse®.

539. Navigating the site brings a list of links to "Articles."[271]

540. One of these articles is entitled "INFUSE® Bone Graft/PEEK Interbody Spacer/Anterior Cervical Plate Clinical Trial Underway." This page was published February 13, 2008 and updated September 07, 2011. For nearly two pages, the article heralds the benefits of Infuse® stating that "[o]ver 500,000 patients have been successfully treated since FDA approval

[270] Neck Surgery http://www.necksurgery.com (also attached hereto as Exhibit 67).
[271] *See* http://www.necksurgery.com/articles.html (also attached hereto as Exhibit 68).

in 2002," and that "[o]ver 15 FDA-approved clinical trials have been performed using INFUSE Bone Graft, making it the most studied biologic agent available to surgeons today."[272]

541. However, 13 of the 15 studies referenced in this "article" have been repudiated for gross bias and inaccurate disclosures of adverse effects.[273]

**N. LEADING SPINE EXPERTS REPUDIATE MEDTRONIC STUDIES**

542. On June 1, 2011 *The Spine Journal*, a leading medical journal in the United States, published a special edition entirely dedicated to addressing serious patient safety and ethical concerns stemming from the use of rhBMP-2 (only one part of Infuse®) in spinal surgeries.[274]

543. *The Spine Journal's* articles discussed the Medtronic Defendants' failure to accurately report the serious side effects from its clinical trials.

544. The Journal's articles discussed the Medtronic Defendants' failure to report that many of the authors of Medtronic-sponsored studies had failed to disclose that they had received substantial compensation and had significant financial ties to Medtronic and that Infuse® can lead to severe side effects.

545. This special edition analyzed thirteen peer-reviewed articles about rhBMP-2 by industry-sponsored authors, including many sponsored by Medtronic, finding that these articles had inaccurately reported the safety and risks associated with rhBMP-2.

546. It is without precedent that the Journal devoted **the entire issue** to setting the record straight by repudiating the prior Medtronic-sponsored Infuse® research.

547. These Medtronic-sponsored studies authored by KOLs universally touted the

[272] *See* http://www.necksurgery.com/articles-infuse_clinical_trial.html (also attached hereto as Exhibit 69).
[273] *See* Exhibit 68.
[274] *Id.*

benefits of the BMP in Infuse® and simultaneously failed to disclose the adverse events associated with its use.

548. In an editorial summarizing the findings of the special issue, five prominent physicians—including spine surgeons at Stanford University—wrote that the earlier Medtronic-sponsored trials and reports were "remarkable for the complete absence of reported rhBMP-2-related clinical adverse events." In fact, the initial studies did not report "a single adverse event associate with rhBMP-2 use in 780 protocol patients."[275]

549. The distinguished editorialists in *The Spine Journal* further remarked, "***none*** of the original estimates of safety for any of the rhBMP-2 applications proved accurate." (Emphasis added).[276]

550. And further, that the studies "underestimated the risks of rhBMP-2 use despite indication from the earliest trials." For example, the Medtronic-sponsored articles falsely omitted mention of adverse events which were evident from the earliest trials, including "inflammatory reactions, adverse back and leg pain events, radiculitis, retrograde ejaculation, urinary retention, bone resorption, and implant displacement."[277]

551. The Medtronic-sponsored studies also omitted mention of sterility and cancer risks associated with rhBMP-2.[278]

552. One of the most damaging aspects of this article was the disclosure that the risk of adverse events associated with rhBMP-2 is actually "***10 to 50 times the original estimates"***

[275] Exhibit 56 at 464, 466.
[276] *Id.* at 463.
[277] *Id.* at 464.
[278] *Id.*

reported in the Medtronic-sponsored peer-reviewed publications as revealed by the unbiased review of the data.[279] (Emphasis added).

553. According to the Medtronic-sponsored studies, BMP adverse events are ***less than one-fortieth (1/40)*** the adverse events of a commonly used anti-inflammatory (such as ibuprofen or aspirin) or antibiotic medications.[280]

554. These Medtronic-sponsored trials suffered from multiple flaws, including idiosyncratic trial design, reporting bias, and peer-review/publication shortfalls.[281]

555. According to *The Spine Journal* editorial, the thirteen Medtronic-sponsored articles reported only successful fusions and low rates of complications with Infuse®. The reviewing physicians opined that the articles "may have promoted widespread and poorly-considered on-label and off-label use, eventual life-threatening complications and deaths."[282]

556. The actions of the Medtronic Defendants failed the medical industry and patients as Dr. Spengler, former Editor-in-Chief of the *Journal of Spinal Disorders*, contends that "the core of our professional faith…is to first do no harm. It harms patients to have biased and corrupted research published. It harms patients to have unaccountable special interests permeate medical research. It harms patients when poor publication practices become business as usual. Yet harm has been done."[283]

[279] *Id.*
[280] Exhibit 65 at 472.
[281] Exhibit 56 at 463.
[282] *Id.*
[283] *Id.* at 466.

557. One author asserts that industry sponsored studies, such as those sponsored by the Medtronic Defendants, have "devolved into information laundering operation."[284] The table below shows that the original 13 studies performed by Medtronic influenced physicians reported zero adverse events out of 780 clinical patients. According to these studies, not a single adverse event was attributed to the BMP in Infuse®. In other words, the product was falsely marketed as perfect.[285]

Original industry-sponsored or industry-associated author rhBMP-2 clinical studies and reported adverse event rates because of rhBMP-2

| Authors | rhBMP-2 Placement | rhBMP-2, n | rhBMP-2 Adverse events (%) | Authors comment regarding rhBMP-2–related observed adverse events in study patients |
|---|---|---|---|---|
| Boden et al. [2] | Anterior interbody (LT-cage, lumbar, rhBMP-2) | 11 | 0 | "There were no adverse events related to the rhBMP-2 treatment" |
| Boden et al. [3] | Posterolateral (lumbar, ± instrumentation) | 20 | 0 | "There were no adverse effects directly related to the rhBMP-2…" |
| Burkus et al. [5] | Anterior interbody (LT-cage, lumbar, INFUSE) | 143* | 0 | "There were no unanticipated device-related adverse events…" |
| Burkus et al. [6] | Anterior interbody (bone dowel, lumbar, INFUSE) | [24]‡ | 0 | "There were no unanticipated adverse events related to the use of INFUSE Bone Graft." (2002) |
| Burkus et al. [39] | | 79 | 0 | None reported (2005) |
| Burkus et al. [40] | Anterior interbody (LT-cage, lumbar, INFUSE) | 277 | 0 | None reported |
| Baskin et al. [7] | Anterior interbody (cervical, INFUSE) | 18 | 0 | "There were no device-related adverse events" |
| Haid et al. [8] | Posterior interbody fusion (lumbar, INFUSE) | 34 | 0 | "No unanticipated device-related adverse events occurred" |
| Boakye et al. [41] | Anterior interbody (cervical, INFUSE) | 24 | 0 | "Analysis of our results demonstrated the safety and efficacy of this combination of cervical spine fusion therapy…. a 100% fusion rate and nonsignificant morbidity" |
| Dimar et al. (2009) | Posterolateral (lumbar, INFUSE, pedicle screws) | 53 | 0 | None reported |
| Glassman et al. [42] | Posterolateral (lumbar, AMPLIFY, and pedicle screws) | [148]† | 0 | None reported |
| Dimar et al. [10] | Posterolateral (lumbar, AMPLIFY, and pedicle screws) | 239 | 0 | "No adverse event that was specifically attributed to the use of rhBMP-2 matrix in the study group was identified" |
| Dawson et al. [11] | Posterolateral (lumbar, INFUSE, and pedicle screws) | 25 | 0 | None reported |
| Total | All types | 780 | 0 | 99% CI <0.5% adverse event rate |

### 1. *The Spine Journal* reveals Medtronic's Agents.

558. The median known financial compensation that the Medtronic Defendants paid to their agent "academic" authors is $12 million-$16 million per study (range, $560,000-$23,500,000).[286]

[284] *Id.* at 466.
[285] Exhibit 65 at 473.
[286] *Id.* at 473.

559. One or more authors were found to have financial relationships with the Medtronic Defendants in excess of $1 million for all studies reporting more than 20 patients who received rhBMP-2.

560. For studies reporting more than 100 patients receiving rhBMP-2, one or more of the so-called "scientific" authors had a financial relationship with the Medtronic Defendants in excess of $10 million.[287]

561. One such study has been openly criticized for inconsistencies thought to be attributed to Medtronic Defendants' financial involvement. In response to the Haid, *et al* study regarding PLIF "off-label" uses, Dr. Spengler, former Editor-in-Chief of the *Journal of Spinal Disorders* commented that he doubted "the [Haid, *et al*.] article would have been written in such positive terms by authors without financial ties to Medtronic."[288]

562. Others have also suspected a fundamental bias in the reporting offered by Medtronic-sponsored studies of rhBMP-2, calling one article "more of a marketing paper than an objective scientific study."[289]

**2. Exaggerating the Morbidity of Traditional Auto-Graft Fusion**

563. Two recent reports suggest that the morbidity of Iliac Crest Bone Graft ("ICBG") harvesting was exaggerated in the Medtronic-sponsored studies described immediately above. Medtronic-sponsored trials estimated that the long-term harm associated with ICBG harvesting was 60%.[290]

564. However, two subsequent independent reports have indicated that patients do not perceive more pain on the operative side of ICBG harvesting, compared with the non-operative

[287] *Id.* at 475.
[288] *Id.* at 486.
[289] *Id.* at 486.
[290] *Id.* at 485.

side, even one year post-surgery.[291]

565. Furthermore, an unsponsored study showed that at two years post-surgery, patients were actually less satisfied with their surgery when BMP was used, than when BMP was not used. The unsponsored study demonstrated that patients had more bothersome symptoms, more functional impairment, and less satisfaction with rhBMP-2 surgery, than those who were treated with non-BMP-2, ICBG harvesting fusion.[292]

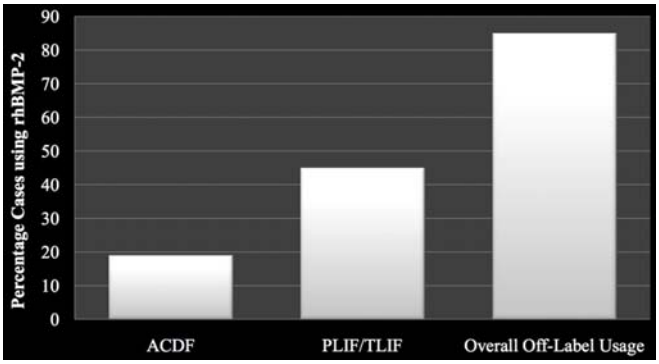
566. The overestimation of morbidity rates by Medtronic-sponsored studies therefore inappropriately exaggerated the potential benefits of Infuse®.

**3. Medtronic grossly underestimated the risks in their sponsored studies**

567. An initial Medtronic-sponsored study failed to report any adverse events related to the use of rhBMP-2 in the cervical spine.

568. Medtronic's failure to accurately report adverse events directly contributed to the prevalence of Infuse® in 2007, where 20% of all Anterior Cervical Discectomy with Fusion ("ACDF") surgeries used Infuse®.

569. The graph below demonstrates the overall use of BMP unapproved by the FDA in both the cervical and lumbar spine.[293]




[291] *Id.* at 485.
[292] *Id.* at 480.
[293] Bozic, M.D., BMP Use: Evaluating Industry-Funded Trials, *available at* http://medicine.yale.edu/core/projects/yodap/463_117257_YODA_Project_Bozic_BMP_Use_02.06.12.pdf (also attached hereto as Exhibit 70). *See also* Exhibit 27 at 3.

570. *The Spine Journal* reported that cervical fusions using rhBMP-2 carried a risk of complications approximately 40% to 50% higher than a cervical fusion conducted without rhBMP-2. A non-sponsored study also reported a 27.5% rate of "clinically significant" cervical swelling in cervical fusions where rhBMP-2 was used.[294]

571. These significant and life-threatening complications arising from the use of rhBMP-2 in the cervical spine prompted the FDA to issue a 2008 Public Health Notification regarding "off-label" use of Infuse® in the cervical spine.[295]

## O. MEDTRONIC FAILED TO ADEQUATELY WARN OF SERIOUS ADVERSE EVENTS

### 1. Unapproved BMP Use Increases Inflammatory Reaction by 500%

572. The pilot study compared the use of BMP in PLIF approach to the traditional surgical method of Iliac Crest Bone Graft ("ICBG"). The "study" was led by Medtronic's agent, Scott Boden, M.D.

573. Medtronic's agent Scott Boden, M.D. reported, "*there were no complications attributable to the rhBMP-2.*"

574. A subsequent review of the study's data by *The Spine Journal* showed that there were in fact adverse effects occurring with BMP-2 at a confidence of 80-90%.

575. Wound problems were at least 10% higher with rhBMP-2 than ICBG in the pilot study, which is likely related to the inflammatory effect of rhBMP-2.

576. A more recent study performed by the Scoliosis Research society found a 500% higher rate of both epidural hematoma and wound complications with rhBMP-2 when used in a posterior approach, contrary to the reports of Dr. Boden.[296]

[294] Exhibit 65 at 482.
[295] *Id.*
[296] *Id.* at 476.

577. The human body can have a severe inflammatory response to the Bone Morphogenetic Protein ("BMP") in Infuse®. As the response progresses, fluid accumulates that causes damage to bone, resorption, cage migration, subsidence (sinking of the cage), compression to nerve roots, and/or leads to a non-union. The inflammatory response from a lumbar surgery and/or rhBMP-2 migrating can damage the cauda equina leading to neurogenic bladder, bowel/bladder incontinence, and retrograde ejaculation.

578. An additional Medtronic-sponsored study published in 2009 reported that the posterolateral approach did not present any adverse events related to rhBMP-2.

579. Subsequent review of the data revealed nearly three times as many back and leg pain adverse events with the use of rhBMP-2.[297]

**2. Medtronic-Sponsored Studies Failed To Report Ectopic Bone Growth**

580. The Medtronic Defendants' agent Regis Haid, M.D. received $25,549,813[298] from Medtronic between 1996 and 2010.

581. Agent Regis Haid, M.D. led a Medtronic-sponsored study that was peremptorily halted.

582. Medtronic's agent Regis Haid, M.D. reported, "no unanticipated device-related adverse events occurred."

583. Medtronic's agent Regis Haid, M.D. asserted that no patient required reoperation because of an rhBMP-2 adverse event.

584. Medtronic's agent Regis Haid, M.D. concluded that the study "confirmed the safety" of rhBMP-2 and suggested that the findings might "eliminate the need" for autograft in

[297] *Id.*
[298] Exhibit 27 at 5.

"successful PLIF."[299]

585. These false and misleading statements and their promotion led to an increase in the use of "off-label" PLIF and TLIF fusions using BMP.[300]

586. A subsequent review of this incomplete study renders a picture riddled with catastrophic adverse events that were not reported by the authors. In fact, ectopic bone growth in the spinal canal or neuroforamina occurred in 24 of 32 rhBMP-2 patients.[301]

587. Shockingly, the physicians noted, "[a]lthough not desirable, bone formation in the spinal canal does not appear to have a discernible effect on the patient outcomes," and "the de novo rhBMP-formed bone occurred predictably, not compressing the neural structures." The authors surprisingly did not find the incidents of bony overgrowth to be a clinically significant concern.[302]

588. An independent surgeon, Dr. Neil Kahanovitz, questioned the authors' interpretations, suggesting that they may have been "overwhelmed by their enthusiasm of using" rhBMP-2 in a PLIF procedure. Dr. Kahanovitz further noted:

> There are lengthy discussions of various trends throughout this study, which imply the superiority of rhBMP over autograft. However, one fact remains: in every clinical measure examined in this study, there were no statistically superior outcomes in the rhBMP group except one, and the clinical significance of this one statistically significant finding is unclear.[303]

589. Further, Dr. Kahanovitz disagreed with the authors' conclusion that the presence of bone growth in the spinal canal and foramina (the two apertures between vertebrae) in those

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[299] *See, e.g.*, Exhibit 56; *see also*, Exhibit 65 at 480.
[300] *Id.*
[301] *Id.*
[302] *Infuse cited in patients' painful bone overgrowth*, Journal Sentinel (June 2011), available at http://www.jsonline.com/watchdog/watchdogreports/124630959.html (attached hereto as Exhibit 71).
[303] Commentary, Neil Kahanovitz, M.D., Haid RW, Branch CL, Alexander JT, Burkus JK. Posterior lumbar interbody fusion using recombinant human bone morphogenetic protein type 2 with cylindrical interbody cages. Spine J. 2004, 538, 527-538, Commentary *available at http://www.bmp2.com.br/BMPLiteraturas/Spine/Spine 2004 Haid INTERFIX PLIF commentary.pdf* (also attached hereto as Exhibit 72).

patients who received rhBMP-2 had no clinical implications. Rather, Dr. Kahanovitz stated that, "most surgeons would be less than enthusiastic to see this statistically significant variable present in the majority of their patients."[304]

590. Ectopic bone growth occurs when bone emerges exuberantly from the rhBMP-2 application site. This bone can compress the spinal cord or exiting nerve roots causing severe pain that radiates to the extremities, numbness/paralysis, urologic, or gastrointestinal injury.

591. A review of the data at two (2) years post-surgery showed patients were less satisfied with rhBMP-2 surgery than those with the traditional ICBG fusion. Patients within the study who were exposed to rhBMP-2 appeared to have more adverse events than the ICBG patients, including functional impairment.[305] Functional impairment can range from complete immobility to neuro deficit. Neuro deficit can progress to paraplegia and occurs when a nerve has been damaged to the point that it is no longer capable of carrying an electrical impulse. This can manifest as paralysis, paresthesia, dysesthesia, numbness, tingling, pins and needles, loss of fine motor skills, or falling down.

592. Medtronic's agent Regis Haid, M.D. failed to include **any** data pertaining to patients requiring an additional surgery to remove ectopic bone growth. Dr. Malone reported that two of his patients involved in the study "had significant posterior bony over-growth impinging on their nerve roots requiring additional surgery." One of these patients required two surgeries "to clear excessive bone formation from his spinal canal." Rather than disclose this critical safety information, Medtronic's agent Regis Haid, M.D. chose to contrive the findings of his study and "confirmed the safety" of rhBMP-2.[306]

[304] *Id.* at 538-539.
[305] Exhibit 65 at 480.
[306] *Id.* at 480-481.

### 3. Failing to Disclose Adverse Events Related To Osteolysis, Subsidence

593. Medtronic-sponsored studies related to rhBMP-2 failed to report adverse events that occurred within the trial period.

594. Subsequent independent reviews of Medtronic-sponsored studies showed osteolysis, subsidence, and reoperation occurred in patients exposed to rhBMP-2.

595. End-plate failure, a catastrophic destruction of the spine, was observed within the first four (4) months after surgery using rhBMP-2 and was not reported by the sponsored authors.[307]

596. Aggressive resorption or osteolysis keeps hardware from attaching to bone, thus leading to a non-union. This can affect the interbody cages or the rods and screws that support a posterolateral fusion. Without the underlying structural support of the fusion hardware, the spine can become grossly unstable, exacerbating degenerative changes and injuring adjacent levels. When the interbody cages fail to fuse to the spine, they can migrate, impinging on the spinal cord or exiting nerve roots, or sink (subside) into the vertebra causing disc space collapse.

597. A further review of an original study lead by Medtronic's agent J. Kenneth Burkus, M.D., published in 2002 and 2004, revealed that subsidence, which occurred in seven patients within two years of the surgery, was not disclosed in the original or initial follow-up study, but rather were only parenthetically reported nearly six years later.[308]

598. In fact, subsidence was not listed at all in the 2002 study. However, four of the seven non-reported patients with subsidence required an additional surgery directly related to

[307] *Id.* at 477.
[308] *Id*. at 478.

their fusion with rhBMP-2. Strikingly, 22 additional surgeries were required for patients in this Burkus study specifically relating to device failure.[309]

599. Medtronic's agent J. Kenneth Burkus, M.D. failed to report **any** of these adverse events or revision surgeries in his Medtronic-sponsored study.[310]

**4. Failing To Disclose Retrograde Ejaculation Due to BMP**

600. Medtronic's agent J. Kenneth Burkus, M.D. failed to report the association of retrograde ejaculation with BMP use in ALIF procedures.[311] Retrograde ejaculation is an injury that affects a male while engaging in sexual intercourse. With retrograde ejaculation, semen is not expelled through the penis, rather it is diverted into the urinary bladder. This process is painful, and can lead to sterility and infection.

601. When Medtronic's agent J. Kenneth Burkus, M.D. was questioned about this in a "Letter to the Editor Inquiry" he dismissed any relationship between BMP and retrograde ejaculation and instead attributed the debilitating adverse event to surgical complication/approach.[312]

602. Data was eventually disclosed regarding the Burkus studies showing a 7.2% rate of retrograde ejaculation among men in ALIF procedures utilizing BMP in comparison to .06% rate in ALIF procedures using the more traditional surgical method of ICBG.[313]

603. The data regarding retrograde ejaculation related to three studies led by Medtronic's agent J. Kenneth Burkus, M.D., who did not release the data until seven years following the original publication. Subsequent studies corroborate a finding that approximately 6% to 7% of men are afflicted with retrograde ejaculation following an ALIF procedure using

[309] *Id.*
[310] *Id.*
[311] *Id.*
[312] *Id.*
[313] *Id.* at 478-479.

rhBMP-2.[314]

### 5. Failing to Report Urogenital Adverse Events from Infuse®

604. Four original Medtronic-sponsored studies related to ALIF procedures and BMP failed to report urogenital adverse events. A subsequent review of the data showed that 7.9% of ALIF procedures performed resulted in a urogenital adverse event.[315] Urogenital adverse events consist of bladder incontinence, neurogenic bladder, retrograde ejaculation, sterility, and erectile dysfunction. Urogenital injuries are caused when the lumbar spine is exposed to Infuse®, and/or the cauda equina is damaged.

605. When a person suffers from urinary incontinence, the nerves are damaged to a point that the urinary sphincters are never triggered to close properly. This renders a person incapable of controlling the flow of urine out of the body.

606. With neurogenic bladder, the effect is the opposite. The nerves are damaged to the point that they cannot release the sphincter, forcing urine to be retained in the bladder. If left untreated, urine can back up into the kidneys, causing a condition called hydronephrosis. When this occurs, the kidneys become saturated with urine causing lasting, and possibly life threatening kidney damage.

607. Similarly, damage to the cauda equina by Infuse® following an ALIF procedure can also result in gastrointestinal injuries. Gastrointestinal injuries caused by Infuse® consist of bowel incontinence, neurogenic bowel (chronic constipation), gastroparesis, and Gastroesophageal reflux disease known as GERD (acid reflux). Like bladder incontinence, bowel incontinence occurs when injury is severe enough that the nerves that controlling the

[314] *Id.*
[315] *Id.* at 479.

rectal sphincters no longer function properly. This makes it difficult or impossible for the person to retain stool.

608. With neurogenic bowel, the opposite effect occurs, whereby the nerves that propel stool through the intestine no longer function properly. The stool remains in the intestine, causing severe and chronic constipation.

609. With gastroparesis, stomach motility is diminished, crippling the body's ability to move food from the stomach into the intestine.

610. With GERD, the nerves are no longer able to regulate the amount of stomach acid that is secreted into the stomach. This stomach acid can erode away at the lower esophagus causing pain and difficulty swallowing, and an increased risk of esophageal cancer.

**6. Failing to Report Adverse Events for "Amplify"**

611. Seeking FDA approval, Medtronic sponsored a study of Amplify, another product manufactured by Medtronic that uses the same rhBMP-2 bone growth protein used in Infuse®.[316] This study was led by Medtronic's agent John Dimar, M.D., who is a surgeon with the Leatherman Spine Center, owned by Norton Hospital in Louisville, Kentucky. Amplify is a tripled dose of rhBMP-2 and was meant to be used in posterolateral spinal fusions.

612. Similar to the previous Medtronic-sponsored studies, Medtronic's agent John Dimar, M.D. reported, "no adverse event that was specifically attributed to the use of rhBMP-2 matrix in the study was identified."[317]

613. A subsequent review of the trial published in 2010 identified several classes of serious adverse events, which appeared to be associated with Amplify but were not reported as

[316] *U.S. nixes Medtronic bone graft product, shares down* (March 10, 2011) *available at* http://www.reuters.com/article/2011/03/10/medtronic-amplify-idUSN1016154820110310 (also attached hereto as Exhibit 73).
[317] *See, e.g.*, Exhibit 56 at 463, *see also*, Exhibit 65 at 482.

such by Medtronic's agent John Dimar, M.D.[318]

614. Medtronic's agent John Dimar, M.D. failed to report the "notably increased cancer rates in the Amplify group." During the study using the higher dose of rhBMP-2, nine (9) new cancers were diagnosed. The sponsored authors did not reveal this finding of increased cancer.[319]

615. In March of 2011, Medtronic disclosed that in December 2010, the FDA sent Medtronic a non-approval letter regarding Amplify.[320] The FDA reviewers stated "[t]he primary safety concern is the increased numbers of cancer events in patients treated with Amplify compared to the control group."[321] A Medtronic spokesman stated that there is "no plausible biological mechanism" for cancer induction.[322] However, lead authors of *The Spine Journal* report, "**the basic biology of growth factor signaling in carcinogenesis suggests that categorical denial is not supportable**."[323] (Emphasis added.)

616. Importantly, doctors often administer BMP for "off-label" use at levels significantly higher than the recommended dosage for on-label procedures, without being informed by Medtronic of the increased risks and dangers, such that the amount of rhBMP-2 in certain surgeries approaches or exceeds that of Amplify®.

617. Furthermore, Dr. Carragee of *The Spine Journal* described the stunning risks of cancer as, "***[a]lmost certainly this is cancer promoting and not a carcinogenic***," he told Reuters in an interview, noting that exposure to a carcinogen takes many more years to result in disease as opposed to a cancer promoting and enabling mechanism found within rhBMP-2. More recent

[318] Exhibit 65 at 482.
[319] *Id.*
[320] Exhibit 73.
[321] *FDA staff: Cancer a concern with Medtronic device* (Jul 23, 2010), *available at* http://www.reuters.com/article/2010/07/23/us-medtronic-spine-idUSTRE66M2U820100723 (also attached hereto as Exhibit 77).
[322] *Id.*; *see also*, Exhibit 65 at 483.
[323] Exhibit 65 at 483.

studies show that there is a 2.5 times greater risk of developing cancer one year after the product was used and a five (5) times greater risk after three years.[324] (Emphasis added.)

### P. SENATORS QUESTION MEDTRONIC ABOUT INFUSE®

618. Despite Medtronic's $40 million dollar settlement in July 2006 with the Department of Justice and Medtronic's $85 million dollar settlement in March 2012 with a group of shareholders, the United States Senate remained concerned with Medtronic's marketing activities and related payments to doctors. Both the United States Senate Special Committee on Aging and the Committee on Finance therefore directed the Medtronic Defendants to answer their questions regarding Infuse.

#### 1. Payments to Doctors Prompted Senators to Inquire re: Infuse®

619. On September 30, 2008, U.S. Senator Herb Kohl, chairman of the Special Committee on Aging, sent a letter to the Medtronic Defendants expressing concern over Medtronic's compliance with the July 2006 Settlement Agreement.[325]

620. Senator Kohl's letter expressed several concerns:

> *Earlier this year, your company's outside counsel provided the Committee with a written account of Medtronic's efforts to comply with the settlement agreement it reached with the United States Department of Justice (DOJ) concerning allegations that Medtronic and its subsidiary improperly compensated surgeons and physicians. That account also addressed the corporate integrity agreement (CIA) that Medtronic and its subsidiary entered into with the Office of the Inspector General of the United States Department of Health and Human Services stemming from those same allegations.*

*****

[324] *Researcher sees cancer risk for Medtronic's Infuse*, Reuters (November 3, 2011), *available at* http://www.reuters.com/article/2011/11/03/us-medtronic-infuse-idUSTRE7A27GT20111103 (also attached hereto as Exhibit 75).

[325] Letter, U.S. Senate, Senate Special Committee on Aging, Herb Kohl to Bill Hawkins, CEO Medtronic (Sep 30. 2008), attached hereto as Exhibit 76, also *available at* http://www.pharmalive.com/sites/pharmalive.com/files/blogs/attachments/kohl-to-medtronic.pdf .

> ***Consequently, it was with concern that I read recent articles, in the Wall Street Journal and elsewhere, which outlined highly disturbing allegations of improper, if not illegal, payments by Medtronic to surgeons and physicians.***
>
> *[C]ontinuing allegations are directly relevant to the Committee's oversight of inappropriate physician compensation practices within the medical device industry. All of the major orthopedic device companies that settled with the DOJ over such allegations were required to publicly reveal information related to their payments to physicians.* ***Medtronic has articulated no specific reasons as to why it should be excused from making the same disclosures***. (Emphasis added).

621. Senator Kohl further noted that in a letter sent by Medtronic's outside counsel, the Medtronic Defendants "both denied that '*improper payments were made to physicians in the first place…much less that improper payments 'have continued.'*" Senator Kohl requested documentation from the Medtronic Defendants' efforts to comply with the July 2006 Settlement Agreement, as well as interviews with corporate witnesses, "*given the ongoing, serious concerns publicly raised regarding the integrity and transparency of Medtronic's physician compensation practices.*"[326] (Emphasis added.)

622. Senator Kohl asked Medtronic to explain "*the circumstances that led Medtronic's former counsel to file suit against the company [alleging improper payments to physicians] and how that matter was subsequently settled.*"[327] (Emphasis added.)

623. On September 30, 2008 U.S. Senator Charles Grassley, on behalf of the Committee on Finance, sent a similar letter[328] to the Medtronic Defendants expressing concern over its marketing of Infuse® and allegations that it had provided kickbacks to physicians who actively promoted Infuse®, noting that:

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[326] *Id.*
[327] *Id.*
[328] Senator Grassley's Letter to Medtronic Regarding Financial Relationships with Physicians, (Oct. 2, 2008), *available at* http://www.finance.senate.gov/newsroom/ranking/release/?id=10014db8-2710-44e9-8398-6bda246f08df.http://www.finance.senate.gov/newsroom/ranking/release/?id=10014db8-2710-44e9-8398-6bda246f08df (also attached hereto as Exhibit 77).

> Last week, the Wall Street Journal (WSJ) [329] reported allegations of financial perks provided to doctors that included "entertainment at a Memphis strip club, trips to Alaska and patent royalties on inventions they played no part in." I would appreciate your assistance in better understanding these allegations and would like to take this opportunity to lay out my specific concerns and questions.
>
> [O]ne of the incentives Medtronic provided physicians was to include them on patents for medical devices and reward them with royalties, even though the physicians may not have contributed to the development of the product.

624. Senator Grassley specifically addressed issues related to Medtronic's marketing of Infuse®:

> [I]t was reported that Medtronic gave payments to physicians, in the form of consulting agreements, as a means of increasing sales of Infuse. The allegations that Medtronic has been disguising these consulting agreements as inducements or kickbacks for physicians to use Infuse are equally troubling. Likewise, this is a practice that I would like to better understand and I would like to know what if anything has changed since these reported events.[330]

625. Senator Grassley also questioned why several lawsuits against the Medtronic Defendants pertaining to Infuse® remained under seal, and indicated that he would like to "better understand the status of these lawsuits and the procedural process that has led to the current situation."[331]

### 2. Senate Committee Launches an Investigation in June 2011

626. The Senate Committee on Finance investigated whether Medtronic continued to misrepresent the adverse events caused by Infuse® and rhBMP-2, as well as the possibility that the Medtronic Defendants improperly influenced the reporting of results collected from clinical trials and reporting regarding rhBMP-2.

627. On June 21, 2011, Senators Charles Grassley and Max Baucus sent a letter to the Medtronic Defendants on behalf of the Senate Committee on Finance requesting that they

[329] Exhibit 42.
[330] Exhibit 77.
[331] *Id.*

produce documents and communication pertaining to "adverse postoperative events and/or medical complications" resulting from the use of rhBMP-2.[332] The letter also requested that the Medtronic Defendants provide "[a] detailed account of payments that Medtronic made to all Infuse® clinical investigators."

628. In the June 21 letter, Senators Grassley and Baucus state:

> *We're extremely troubled by press reports suggesting that doctors conducting clinical trials examining the safety and effectiveness of* Infuse® *on behalf of Medtronic were aware that* Infuse®*, a treatment commonly used in spinal surgery, may cause medical complications, but failed to report this in the medical literature. This issue is compounded by the fact that some clinical investigators have substantial financial ties to Medtronic.*[333] (Emphasis added.)

629. The Senators' letter also addressed concern related to inconsistencies arising from a Medtronic-funded study asserting:

> that 75% of bone morphogenic protein 2 (BMP-2) patient experienced ectopic growth, where potentially harmful bone growth occurs outside of the fusion area. *The authors, who had financial ties to Medtronic, 'concluded that 'although not desirable,' the ectopic bone growth "did not appear to have an ill effect on patients."* However, in a separate 2008 study conducted without financial ties to Medtronic, 'neurological impairment occurred in five patients who had the same ectopic bone formation.'[334] (Emphasis added.)

630. The Senators cited an article in *The New York Times* that reported a recent study "found that men treated with Infuse developed a condition that causes temporary or permanent sterility at a far higher rate than men who received a bone graft." The Senators noted that this link to sterility was not reported in the original Medtronic-funded study.[335]

631. The Senators added:

> We are also concerned that other severe side-effects of Infuse® and similar bone-growth products developed by Medtronic may have been unreported or under-

[332] Letter from Charles Grassley & Max Baucus to Medtronic (June 21, 2011), *available at* http://www.finance.senate.gov/newsroom/chairman/release/?id=a7e974b6-b4b6-4e2c-a738-edefac30fcb6 (also attached hereto as Exhibit 78).
[333] *Id.*
[334] *Id.*
[335] *Id.*

> reported in clinical literature. *Reports have linked* Infuse® *to potentially fatal swelling in the neck and throat, and radiating leg pain. Concerns have also been expressed about a potential link to cancer.*[336] (Emphasis added.)

**3. Senate Also Inquires Into Recalls, and Post-Market Surveillance**

632. Senators Herb Kohl, Charles E. Grassley, and Richard Blumenthal addressed further concerns over the Medtronic Defendants' oversight of recalls and post-market surveillance of Infuse®, in a letter dated December 13, 2011:[337]

> [W]e take seriously our responsibility to protect the interests of our nation's health care consumers. We are writing today to request information on how your company handles recalls and post-marketing surveillance on your products…
>
> All health care consumers in the United States depend on companies such as Medtronic to deliver high-quality, safe, and effective products. Recently, your company has experienced safety issues, such as with your product Infuse. A researcher at Stanford University School of Medicine found a higher risk of cancer associated with Infuse, and there have been allegations that researchers who received funds from Medtronic, sometimes millions of dollars, did not report negative finding from clinical trials. We are concerned that consumers who have long relied on your products, are being adversely affected by these issues, both through the on-label and off-label use of the product.

633. Further, the Senators requested additional information pertaining to Medtronic's promotion of the "off-label" use of Infuse® :

> …
>
> 3. How does your company derive failure rates or rates of serious adverse events of medical devices? What is the current estimate of the serious adverse event rate of Infuse? Please give rates for both on-label and off-label usage.
>
> 4. How many individual complaints has your company received about Infuse to date? … What percentage of these complaints were for off-label usage?
>
> …

[336] *Id.*

[337] Letter from US Senate to Omar Ishrak, Medtronic CEO (Dec.13, 2011), *available at* http://www.grassley.senate.gov/about/upload/Medtronic.pdf (also attached hereto as Exhibit 79).

7. Do you require physicians who receive funds from your company to disclose those payments to their patients before the patients receive one of your medical devices? If not, why not?[338]

**Q. SENATORS REVEAL MANIPULATION OF SCIENTIFIC STUDIES**

634. In October 25, 2012, the U.S. Senate concluded its official investigation of the Medtronic Defendant, which sought to determine whether it had improperly influenced peer-reviewed studies on Infuse®. In response to demands made during the investigation, the Medtronic Defendants provided over 5,000 documents related to the 13 BMP studies identified by *The Spine Journal* as sponsored by Medtronic.[339]

635. The 16-month inquiry led the U.S. Senate to conclude:

a. "Medtronic was heavily involved in drafting, editing, and shaping the content of medical journal articles authored by its physician consultants who received significant amounts of money through royalties and consulting fees from Medtronic. The company's significant role in authoring or substantively editing these articles was not disclosed in the published articles. Medical journals should ensure industry role contributions be fully disclosed."

b. "Medtronic paid a total of approximately $210 million to physician authors of Medtronic-sponsored studies from November 1996 through December 2010 for consulting, royalty, and other miscellaneous arrangements."

c. "An e-mail exchange shows that a Medtronic employee recommended against publishing a complete list of adverse events possibly associate with Infuse in a 2005 Journal of Bone and Joint Surgery articles."

d. "Medtronic officials inserted language into studies that promoted InFuse as a better technique than taking a bone graft from the pelvic bone (autograft technique) by emphasizing the pain of the autograft technique."

e. Documents indicate that Medtronic prepared Dr. Hal Mathew's remarks to the U.S. Food and Drug Administration (FDA) advisory panel meeting prior to InFuse being approved. At the time, Dr. Mathews was a private physician but was hired as a vice president at Medtronic in 2007.

f. Medtronic documents show the company unsuccessfully attempted to adopt weaker safety rules for a clinical trial studying InFuse in the cervical spine

[338] *Id.*
[339] Exhibit 27 at 1.

that would have allowed the company to continue the trial in the event that patients experienced severe swelling in the neck. [340]

636. These findings prompted Senator Baucus to state "patients are at serious risk when companies distort the facts the way Medtronic has." [341]

637. The U.S. Senate Report revealed the following multi-million dollars payments to physicians, totaling approximately $210,000,000 paid by Medtronic in the below chart. [342]

| Year | Scott D. Boden | Charles L. Branch | J. Kenneth Burkus | Concept Properties, LLC [18] | Curtis A. Dickman |
|---|---|---|---|---|---|
| 1996 | $18,750.00 | — | — | — | — |
| 1997 | $75,000.00 | — | — | — | $5,003.70 |
| 1998 | $75,000.00 | $140,703.15 | $18,700.00 | — | $73,239.25 |
| 1999 | $86,957.00 | $49,238.87 | $34,712.12 | — | $130,352.64 |
| 2000 | $75,000.00 | $104,495.00 | $29,285.75 | — | $41,419.50 |
| 2001 | $73,750.00 | $150,000.00 | $149,920.00 | $636,182.00 | $56,960.00 |
| 2002 | $80,000.00 | $201,997.75 | $220,539.50 | $1,028,882.00 | $72,881.00 |
| 2003 | $82,500.00 | $180,219.99 | $268,742.50 | $1,226,179.00 | $316,215.00 |
| 2004 | $138,500.00 | $175,473.78 | $360,447.78 | $4,992,137.00 | $320,045.99 |
| 2005 | $1,364,100.00 | $127,087.44 | $331,070.44 | $13,141,165.00 | $339,338.00 |
| 2006 | $1,782,550.00 | $136,390.58 | $613,849.71 | $8,842,157.00 | $401,138.77 |
| 2007 | $3,400,875.00 | $114,159.39 | $719,281.84 | $9,683,098.00 | $383,192.00 |
| 2008 | $21,543,052.00 | $487,688.50 | $1,928,503.35 | $9,159,891.00 | $388,248.00 |
| 2009 | — | $460,319.35 | $732,563.85 | $7,117,112.00 | $355,809.00 |
| 2010 | — | $827,851.81 | $972,719.99 | $9,004,465.00 | $389,099.00 |
| Total | $28,796,034.00 | $3,155,625.61 | $6,380,336.83 | $64,831,268.00 | $3,272,941.85 |

| Year | John R. Dimar, III | Steven D. Glassman | Matthew F. Gornet | Regis W. Haid, Jr. | John G. Heller |
|---|---|---|---|---|---|
| 1996 | $6,250.00 | $6,250.00 | — | — | — |
| 1997 | $27,000.00 | $25,000.00 | $1,880.00 | $27,500.00 | — |
| 1998 | $50,000.00 | $50,000.00 | — | $216,842.44 | $10,892.00 |
| 1999 | $52,022.65 | $52,216.41 | $29,900.00 | $1,019,832.54 | $70,817.57 |
| 2000 | $50,000.00 | $50,976.43 | $16,369.97 | $1,507,242.15 | $30,000.00 |
| 2001 | $188,428.00 | $194,528.00 | $15,128.00 | $1,394,390.61 | $37,975.10 |
| 2002 | $100,100.00 | $71,750.00 | $4,762.00 | $1,669,745.11 | $1,161.73 |
| 2003 | $116,283.65 | $138,941.44 | $10,194.00 | $1,957,742.86 | $49,191.50 |
| 2004 | $104,043.67 | $146,137.07 | $17,924.00 | $2,484,450.94 | $42,957.44 |
| 2005 | $147,207.99 | $248,019.59 | $67,763.93 | $2,473,518.00 | $154,835.70 |
| 2006 | $236,306.95 | $155,753.16 | $238,787.49 | $2,454,569.00 | $149,215.39 |
| 2007 | $130,767.60 | $257,926.16 | $649,542.33 | $2,626,576.07 | $330,792.15 |
| 2008 | $234,094.50 | $187,605.50 | $1,181,039.87 | $2,467,911.23 | $288,957.11 |
| 2009 | $160,551.00 | $88,139.80 | $892,500.87 | $2,525,743.88 | $255,236.24 |
| 2010 | $163,310.20 | $75,019.80 | $859,983.76 | $2,723,749.13 | $352,404.36 |
| Total | $1,766,366.21 | $1,748,263.36 | $3,985,776.22 | $25,549,813.96 | $1,774,436.29 |

| Year | Inspire, LLC [19] | Gerald E. Rodts, Jr. | Volker Sonntag | Ensor E. Transfeldt | Thomas A. Zdeblick |
|---|---|---|---|---|---|
| 1996 | — | — | — | $12,500.00 | $95,185.34 |
| 1997 | — | — | $34,745.92 | $50,000.00 | $422,668.65 |
| 1998 | — | $25,065.54 | $207,622.16 | $56,196.00 | $838,794.89 |
| 1999 | — | $44,748.08 | $795,053.91 | $61,219.28 | $1,131,463.17 |
| 2000 | — | $ 152,496.47 | $1,756,041.55 | $56,170.90 | $1,037,381.49 |
| 2001 | — | $140,343.39 | $1,036,993.00 | $71,117.56 | $1,984,356.45 |
| 2002 | — | $172,278.04 | $1,646,050.49 | $115,315.16 | $3,471,930.41 |
| 2003 | — | $142,025.68 | $1,904,689.00 | $258,912.62 | $4,580,361.62 |
| 2004 | — | $161,149.02 | $2,728,639.00 | $299,477.72 | $4,447,269.00 |
| 2005 | — | $303,877.98 | $2,202,595.00 | $30,474.70 | $3,950,516.08 |
| 2006 | — | $396,139.57 | $2,090,998.00 | $206,388.76 | $3,469,863.71 |
| 2007 | $247,365.00 | $629,451.53 | $2,163,661.90 | $722,779.00 | $2,961,272.00 |
| 2008 | $329,998.00 | $581,984.26 | $2,271,477.00 | $548,584.74 | $2,521,170.00 |
| 2009 | $698,829.00 | $432,403.00 | $1,772,361.00 | $483,254.00 | $1,582,156.00 |
| 2010 | $1,632,813.00 | — | $2,241,156.00 | $589,930.00 | $1,674,351.00 |
| Total | $2,909,005.00 | $3,181,962.56 | $22,852,083.93 | $3,562,320.44 | $34,168,739.81 |

[340] U.S. Senate, Committee on Finance, Press Release, *Baucus-Grassley Investigation into Medtronic Reveals Manipulated Studies, Close Financial Ties with Researchers*, (October 2012), *available at* http://www.finance.senate.gov/newsroom/chairman/release/?id=b1d112cb-230f-4c2e-ae55-13550074fe86 (also attached hereto as Exhibit 80).

[341] *Id.*

[342] Exhibit 27 at 5.

638. In response to the Senate's finding that the Medtronic Defendants failed to disclose payments of enormous sums of money to physicians, many of whom were responsible for publishing articles regarding Infuse®, articles which have now been exposed by the U.S. Senate investigation to have been manipulated by Medtronic intentionally omitting the reporting of adverse events, Michael Heggeness and Charles Mick, president and first vice president of the North American Spine Society, applauded the Senate Committee's report.

639. Significantly, the two preeminent surgeons' remarks directly debunked what is claimed by the Medtronic Defendant to be the "learned intermediary" defense: "If surgeons had known that the lead authors of the 13 original studies on InFuse had received payments ranging from $1.7 million to $64 million from Medtronic and that its marketing employees were co-authors and co-editors, would they have been so eager to use InFuse on their patients?"[343]

640. As Doctors Michael Heggeness and Charles Mick observed, there is no way that a surgeon making the decision on what procedure and/or medical device to use for their patients, would use a procedure and/or medical device where the manufacturer of the device had paid the lead authors of the studies amounts ranging from $1.7 million to $64 million, and where the manufacturers own marketing employees were "secret" co-authors and co-editors of those very studies and resulting in the material distortion of the actual findings and results of those "studies."

641. The federal judiciary has recognized a genuine risk that financial conflicts of interest induce bias in scientific research. The Federal Judicial Center's key reference guide for judges considering scientific issues in their cases explains, "[j]udges and juries . . . must consider

[343] McCarthy, Michael, *US firm accused of manipulating journal articles and paying millions to authors*, (Oct 2012), BMJ 2012, *available at* http://www.bmj.com/content/345/bmj.e7299 (also attached hereto as Exhibit 81).

financial conflicts of interest when assessing scientific testimony. The threshold for pursing the possibility of bias must be low."[344]

642. Research published in the *New England Journal of Medicine*, as well as other surveys, show that information brought by industry representatives to physicians impacts medical decision-making.[345] The Medtronic Defendants' misleading marketing of BMP to physicians, including Plaintiffs' surgeons, was designed to impact surgeons' selections with the goal of expanding the market for Infuse® beyond FDA-approved uses. The Medtronic Defendants consciously created this misleading marketing campaign even though they knew that it would expose patients, including Plaintiffs herein, to increased risks of danger and serious injuries.

643. The published articles listed below were repudiated by *The Spine Journal* and the authors' financial relationships with the Medtronic Defendants were only discovered through their investigation and disclosed by the U.S. Senate Report.

644. The Medtronic Defendants paid their KOL Scott Boden, M.D. $28,796,034.00 from 1996-2010.[346]

a. **Scott Boden** and Thomas A. Zdeblick et al., *The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans*, 25 J. Spinal Disord. 376 (2000).

b. **Scott Boden** and John G. Heller et al., *Use of recombinant human bone morphogenetic protein-2 to achieve posterolateral lumbar spine fusion in humans: a prospective, randomized clinical pilot trial: 2002 Volvo Award in clinical studies*; 27 Spine 2662 (2002).

[344] Reference Manual on Scientific Evidence, xiii, (2011) *available at* http://www.fjc.gov/public/pdf.nsf/lookup/SciMan3D01.pdf/$file/SciMan3D01.pdf (pages cited attached hereto as Exhibit 82).
[345] Bernard Lo, M.D., Serving Two Masters – Conflicts of Interest in Academic, *N Engl J Med 2010, available at* http://www.nejm.org/doi/full/10.1056/NEJMp1000213 (also attached hereto as Exhibit 83).
[346] Exhibit 27.

c. **Scott Boden**, Steven Glassman, John Dimar, Kenneth Burkus et al., *The efficacy of rhBMP-2 for posterolateral lumbar fusion in smokers*, 32 Spine 1693 (2007).

645. Medtronic paid its KOL Charles Branch, M.D. $3,155,625.61 from 1996-2010.[347]

a. **Charles Branch**, Regis Haid, Kenneth Burkus and J.T. Alexander., *Posterior lumbar interbody fusion using recombinant human bone morphogenetic protein type 2 with cylindrical interbody cages*, 4 Spine J. 527 (2004).

646. Medtronic paid its KOL J. Kenneth Burkus, M.D. $6,380,336.83 from 1996-2010.[348]

a. **J. Kenneth Burkus**, Michael F. Gornet, Curtis A. Dickman and Thomas A. Zdeblick, *Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages*, 15 J. Spinal Disord. Tech. 337 (2002).

b. **J. Kenneth Burkus**, Ensor E. Transfeldt et al., *Clinical and radiographic outcomes of anterior lumbar interbody fusion using recombinant human bone morphogenic protein-2*, 27 Spine 2396 (2002).

c. **J. Kenneth Burkus**, S.E. Heim, Michael F. Gornet and Thomas A. Zdeblick, *Is INFUSE bone graft superior to autograft bone? An integrated analysis of clinical trials using the LT-Cage lumbar tapered fusion device*, 16 J. Spinal Disord. Tech. 113 (2003).

d. **J. Kenneth Burkus**, Charles Branch, J.T. Alexander and Regis Haid, *Posterior lumbar interbody fusion using recombinant human bone morphogenetic protein type 2 with cylindrical interbody cages*, 4 Spine J. 527 (2004).

e. **J. Kenneth Burkus** and Matthew Gornet et al., *Use of rhBMP–2 in combination with structural cortical allografts surgery: clinical and radiographic outcomes in anterior lumbar spinal fusion*, 87 J. Bone Joint Surg. Am. 1205 (2005).

f. John R. Dimar, Steven D. Glassman, **J. Kenneth Burkus** and Leah Y. Carreon, *Clinical outcomes and fusion success at 2 years of single-level instrumented posterolateral fusions with recombinant human bone morphogenic protein-2/compression resistant matrix versus iliac crest bone graft*, 31 Spine 2534 (2006).

[347] *Id.*
[348] *Id.*

g. **J. Kenneth Burkus**, Steven Glassman and John Dimar et al. *The efficacy of rhBMP–2 for posterolateral lumbar fusion in smokers*, 32 Spine 1693 (2007).

h. John Dimar, Steven Glassman, **J. Kenneth Burkus**, et al. *Clinical and radiographic analysis of an optimized rhBMP–2 formulation as an autograft replacement in posterolateral lumbar spine arthrodesis*, 91 J. Bone Joint Surg. Am. 1377 (2009).

i. **J. Kenneth Burkus** and Steven Glassman et al., *Recombinant human bone morphogenetic protein–2 on an absorbable collagen sponge with an osteoconductive bulking agent in posterolateral arthrodesis with instrumentation. A prospective randomized trial*, 9 J. Bone Joint Surg. Am. 1604 (2009).

647. Medtronic paid its KOL Curtis Dickman, M.D. $3,272,941.85 from 1996-2010.[349]

a. J. Kenneth Burkus, Michael F. Gornet, **Curtis A. Dickman** and Thomas A. Zdeblick, *Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages*, 15 J. Spinal Disord. Tech. 337 (2002).

648. Medtronic paid its KOL John Dimar, M.D. $1,766,366.21 from 1996-2010. Medtronic also paid Concept Properties, LLC, a limited liability corporation owned in part by Medtronic's KOL John Dimar, M.D., $64,831,268.00 from 1996-2010.[350]

a. **John R. Dimar**, Steven D. Glassman, J. Kenneth Burkus and Leah Y. Carreon, *Clinical outcomes and fusion success at 2 years of single-level instrumented posterolateral fusions with recombinant human bone morphogenic protein-2/compression resistant matrix versus iliac crest bone graft*, 31 Spine 2534 (2006).

b. Steven D. Glassman, J. Kenneth Burkus and **John R Dimar** et al. *The efficacy of rhBMP–2 for posterolateral lumbar fusion in smokers*. 32 Spine 1693 (2007).

c. **John R Dimar**, Steven D Glassman, J Kenneth Burkus, Philip W Pryor, James W Hardacker and Leah Y. Carreon, *Clinical and radiographic analysis of an optimized rhBMP-2 formulation as an autograft replacement in posterolateral spine arthrodesis*, 91 J. Bone Joint Surg. Am. 1377 (2009).

[349] *Id.*
[350] *Id.*

649. Medtronic paid its KOL Steven Glassman, M.D. $1,748,263.36 from 1996-2010. Medtronic also paid Concept Properties, LLC, a limited liability corporation owned in part by Medtronic's KOL Steven Glassman, M.D., $64,831,268.00 from 1996-2010.[351]

a. John R. Dimar, **Steven D. Glassman**, Kenneth J. Burkus and Leah Y. Carreon, *Clinical outcomes and fusion success at 2 years of single-level instrumented posterolateral fusions with recombinant human bone morphogenic protein-2/compression resistant matrix versus iliac crest bone graft*, 31 Spine 2534 (2006).

b. **Steven D. Glassman**, J. Kenneth Burkus and John Dimar et al. *The efficacy of rhBMP–2 for posterolateral lumbar fusion in smokers*. 32 Spine 1693 (2007).

c. John R Dimar, **Steven D Glassman**, J Kenneth Burkus, Philip W. Pryor, James W Hardacker and Leah Y. Carreon, *Clinical and radiographic analysis of an optimized rhBMP-2 formulation as an autograft replacement in posterolateral spine arthrodesis*, 91 J. Bone Joint Surg. Am. 1377 (2009).

d. J. Kenneth Burkus and **Steven Glassman** et al., *Recombinant human bone morphogenetic protein–2 on an absorbable collagen sponge with an osteoconductive bulking agent in posterolateral arthrodesis with instrumentation. A prospective randomized trial*, 9 J. Bone Joint Surg. Am. 1604 (2009).

650. Medtronic paid its KOL Matthew Gornet, M.D. $3,985,776.22 from 1996-2010. Gornet Enterprises, LLC is a limited liability corporation owned in part by Medtronic's Agent Matthew Gornet, M.D.[352]

a. J. Kenneth Burkus, **Matthew F. Gornet**, Curtis A. Dickman and Thomas A. Zdeblick, *Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages*, 15 J. Spinal Disord. Tech. 337 (2002).

b. J. Kenneth Burkus, S.E. Heim, **Michael F. Gornet** and Thomas A. Zdeblick, *Is INFUSE bone graft superior to autograft bone? An integrated analysis of clinical trials using the LT-Cage lumbar tapered fusion device*, 16 J. Spinal Disord. Tech. 113 (2003).

c. J. Kenneth Burkus and **Matthew Gornet** et al., *Use of rhBMP–2 in combination with structural cortical allografts surgery: clinical and*

[351] *Id.*
[352] *Id.*

*radiographic outcomes in anterior lumbar spinal fusion*, 87 J. Bone Joint Surg. Am. 1205 (2005).

651. Medtronic paid its KOL Regis Haid, M. D. $25,549,813.96 from 1996-2010.[353]

a. Charles Branch, **Regis Haid**, Kenneth Burkus and J.T. Alexander., *Posterior lumbar interbody fusion using recombinant human bone morphogenetic protein type 2 with cylindrical interbody cages*, 4 Spine J. 527 (2004).

b. Gerald E. Rodts, **Regis Haid** et al., *Anterior cervical discectomy and fusion involving a polyetheretherketone spacer and bone morphogenetic protein*, 2 J. Neurosurg. Spine 521 (2005).

652. Medtronic paid its KOL John G. Heller, M.D. $1,774,436.29 from 1996-2010.[354]

a. Scott Boden and **John G. Heller** et al., *Use of recombinant human bone morphogenetic protein-2 to achieve posterolateral lumbar spine fusion in humans: a prospective, randomized clinical pilot trial: 2002 Volvo Award in clinical studies*; 27 Spine 2662 (2002).

653. Medtronic paid its KOL Gerald E. Rodts, Jr., M.D. $3,181,962.56 from 1996-2010.[355]

a. **Gerald E. Rodts,** Regis Haid et al., *Anterior cervical discectomy and fusion involving a polyetheretherketone spacer and bone morphogenetic protein*, 2 J. Neurosurg. Spine 521 (2005).

654. Medtronic paid its KOL Volker Sonntag, M.D. $22,852,083.93 from 1996-2010.[356]

a. **Volker Sonntag**, et al., *A prospective, randomized, controlled cervical fusion study using recombinant human bone morphogenetic protein–2 with the CORNERSTONE–SR allograft ring and the ATLANTIS anterior cervical plate*, 28 Spine 1219 (2003).

655. Medtronic paid its KOL Ensor Transfeldt, M.D. $3,562,320.44 from 1996-2010.

Additionally, Medtronic paid Inspire, LLC, a limited liability corporation owned in part by Medtronic's KOL Ensor Transfeldt, M.D., $2,909,005.00.[357]

[353] *Id.*
[354] *Id.*
[355] *Id.*
[356] *Id.*

a. J. Kenneth Burkus, **Ensor E. Transfeldt** et al., *Clinical and radiographic outcomes of anterior lumbar interbody fusion using recombinant human bone morphogenic protein-2*, 27 Spine 2396 (2002).

656. Medtronic paid its KOL Thomas A. Zdeblick, M.D. $34,168,739.81 from 1996-2010.[358]

a. Scott Boden and **Thomas A. Zdeblick** et al., *The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans*, 25 J. Spinal Disord. 376 (2000).

b. J. Kenneth Burkus, Michael F. Gornet, Curtis A. Dickman and **Thomas A. Zdeblick**, *Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages*, 15 J. Spinal Disord. Tech. 337 (2002).

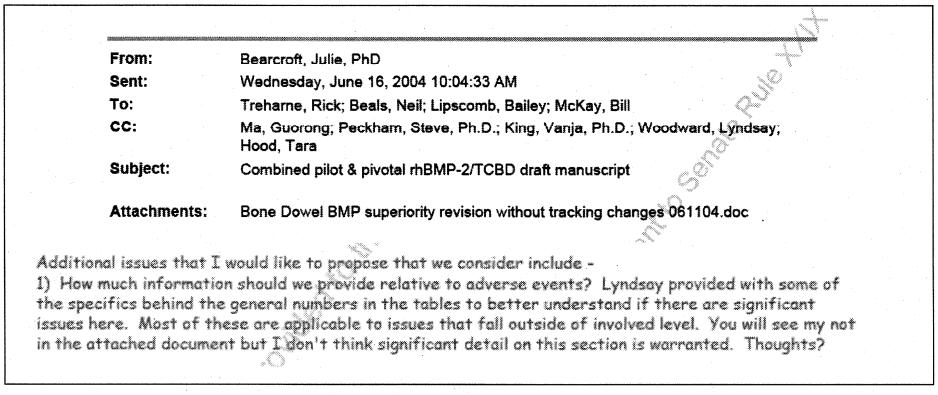
c. J. Kenneth Burkus, S.E. Heim, Michael F. Gornet and **Thomas A. Zdeblick**, *Is INFUSE bone graft superior to autograft bone? An intergrated analysis of clinical trials using the LT-Cage lumbar tapered fusion device*, 16 J. Spinal Disord. Tech. 113 (2003).

### 1. Conspiring With Medtronic's Agent J. Kenneth Burkus, M.D.

657. Medtronic officials recommended against publishing "a complete list of adverse events possibly associated with Infuse."[359] In 2004, Dr. Julie Bearcroft, the Director of Technology Management in Medtronic's Biologics Marketing Department, wrote an email to other high-level Medtronic employees stating:[360]

> *I have made some significant changes to this document (some at the request of Dr. Burkus) both in format and content. . . .**How much information should we provide relative to adverse events?. . .You will see my [note] in the attached document but I don't think significant detail on this section is warranted.*** (Emphasis added.)

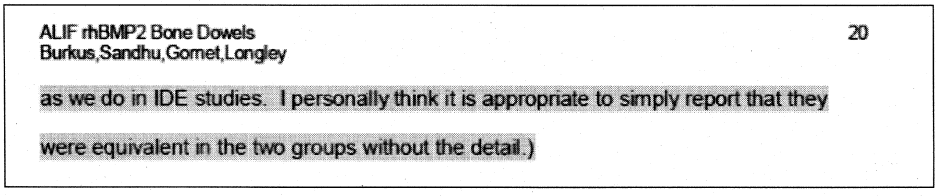
[357] *Id.*
[358] *Id.*
[359] Exhibit 27 at 2.
[360] *Id*. at 9.



**From:** Bearcroft, Julie, PhD
**Sent:** Wednesday, June 16, 2004 10:04:33 AM
**To:** Treharne, Rick; Beals, Neil; Lipscomb, Bailey; McKay, Bill
**CC:** Ma, Guorong; Peckham, Steve, Ph.D.; King, Vanja, Ph.D.; Woodward, Lyndsay; Hood, Tara
**Subject:** Combined pilot & pivotal rhBMP-2/TCBD draft manuscript

**Attachments:** Bone Dowel BMP superiority revision without tracking changes 061104.doc

Additional issues that I would like to propose that we consider include -
1) How much information should we provide relative to adverse events? Lyndsay provided with some of the specifics behind the general numbers in the tables to better understand if there are significant issues here. Most of these are applicable to issues that fall outside of involved level. You will see my not in the attached document but I don't think significant detail on this section is warranted. Thoughts?



ALIF rhBMP2 Bone Dowels 20
Burkus,Sandhu,Gornet,Longley

as we do in IDE studies. I personally think it is appropriate to simply report that they were equivalent in the two groups without the detail.)

658. The prior draft of the paper included material adverse events. However, Medtronic's KOL J. Kenneth Burkus, M.D., deliberately and intentionally deleted these adverse events from the final published report.

659. This was confirmed by the findings of the Senate Investigation. The U.S. Senate Committee on Finance found that "**the adverse events observed in the allograft trial were observed and formatted in a table, but following the advice of Bearcroft, the table of was not included in the published paper.**"[361] (Emphasis added.)

660. *The Spine Journal* scrutinized this particular Medtronic-sponsored study for failing to report any adverse events and for neglecting to mention that Medtronic funded three of the physician authors with more than $12 million.

661. According to the Senate Report, "**Medtronic recommended against including information in the study** that was ultimately revealed to have an association between Infuse®

[361] *Id*. at 10.

and weakening that could lead to collapse of the bone and implant and required patients undergo additional surgery."[362] (Emphasis added.)

**2. Over-Emphasizing Pain in Alternative Spinal Treatments**

662. Medtronic directly edited and even ghostwrote publications, which to the outside medical world, were ostensibly written by the named authors, promoting the use of BMP over the use of a bone graft by over stressing the pain at the donor site when using a bone graft and omitting the injuries that were actually observed when BMP was used.

663. The Senate Report uncovered documents that show "**Medtronic edited draft publications to stress the pain patients experienced from undergoing a bone graft procedure** instead of receiving InFuse."[363]

664. Neil Beals, Medtronic's Vice President of Biologic Marketing, sent emails to authoring physicians in two separate studies suggesting that more emphasis be placed on the elimination of "donor site" pain when the surgeon elected to use Infuse® instead of a bone graft.[364]

665. Following these studies, Medtronic's website promoted the benefits of Infuse® over traditional iliac crest bone grafts stating, that "[a]ccording to numerous studies, the harvesting procedure is actually more painful than the fusion itself, and nearly a third of patients experience hip pain two years following surgery."[365] However these studies only included such information after persistent insistence by the Medtronic's Vice President.

[362] *Id.* at 9.
[363] *Id.* at 11. (Emphasis added.)
[364] *Id.*
[365] *Id.; see also,* Exhibit 31.

666. Vice President Beals worked directly with Medtronic's KOL J. Kenneth Burkus, M.D. and encouraged him to include information emphasizing the pain related to the "donor site."[366]

667. After reviewing a draft of Medtronic's KOL J. Kenneth Burkus, M.D.'s study, Vice President Beals emailed Dr. Burkus stating "a bigger deal should be made of elimination of donor site pain with Infuse." [367]

668. Nearing publication, Vice President Beals again sent an email suggesting***, "would it be appropriate to make a bigger deal out of donor site pain."***[368]

| | |
|---|---|
| **From:** | Neil Beals |
| **Sent:** | Friday, March 8, 2002 04:04:43 PM |
| **To:** | J. Kenneth Burkus |
| **CC:** | Tom Zdeblick M.D.; Tara Hood; Bailey Lipscomb; Pete Wehrly; Bill Martin; Clark Charlton; Julie Bearcroft; [redacted] |
| **Subject:** | FW: Open LT BMP manuscript |
| **Attachments:** | Final revisions OPEN LTCAGE BMP.1.doc |

- would it be appropriate to make bigger deal out of donor site pain and include more discussion and references?

669. A sentence, at the apparent direct request of Vice President Beals, was incorporated into the final published study stating, "[t]he use of rhBMP-2 is associated with high fusion rates without the need for harvesting bone graft from the iliac crest and exposing the patient to adverse effects associated with that procedure."[369]

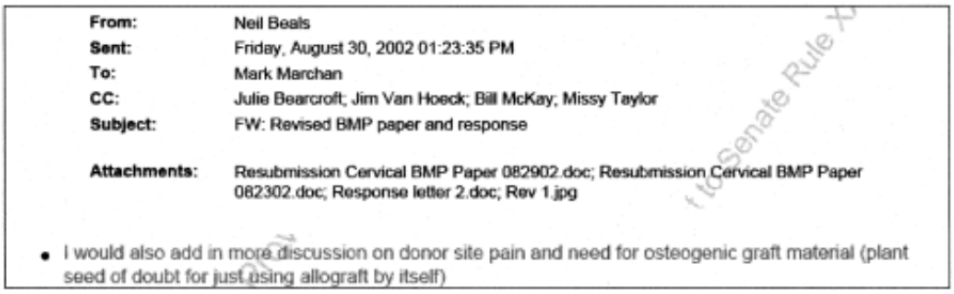
670. Again, Vice President Beals inserted comments encouraging discussion of donor site pain on a draft article co-authored by another Medtronic KOL Volker Sonntag, M.D.

[366] Exhibit 27 at 11.
[367] *Id.* at 11-12.
[368] *Id.* (Emphasis added.)
[369] *Id.* at 12.

671. According to the Senate Report, the Medtronic Defendants paid their KOL Volker Sonntag, M.D. nearly $23 million dollars. The article co-written by Dr. Sonntag stated, "[b]y 12 months after surgery, the patients [sic] graft-site pain resolved…and no patient complained about the graft-site appearance."[370]

672. Despite this finding, Vice President Beals inserted comments on the draft stating, *"ALTHOUGH THE PATIENTS DID NOT COMPLAIN ABOUT APPEARANCE DIDN'T SOME STILL EXPERIENCE PAIN AT THE DONOR SITE? SEEMS LIKE RESIDUAL EFFECT OF DONOR SITE SHOULD BE NOTED."* [371] (Emphasis in original).

673. And if KOL Volker Sonntag, M.D. didn't get it from the above communication from Vice President Beals, Beals wrote a subsequent email further thrusting the Medtronic Defendants' involvement in the ghostwriting of the published studies. In this subsequent email, Medtronic's Vice President wrote, "I would also add in more discussion on donor site pain and need for osteogenetic graft material ***(plant seed of doubt for just using allograft by itself)***."[372] (Emphasis added).



**From:** Neil Beals
**Sent:** Friday, August 30, 2002 01:23:35 PM
**To:** Mark Marchan
**CC:** Julie Bearcroft; Jim Van Hoeck; Bill McKay; Missy Taylor
**Subject:** FW: Revised BMP paper and response

**Attachments:** Resubmission Cervical BMP Paper 082902.doc; Resubmission Cervical BMP Paper 082302.doc; Response letter 2.doc; Rev 1.jpg

- I would also add in more discussion on donor site pain and need for osteogenic graft material (plant seed of doubt for just using allograft by itself)

674. These suggestions were incorporated into the final published version of the scientific article without mention of the nearly $23 million dollars the Medtronic Defendants

[370] *Id.*
[371] *Id.* at 12.
[372] *Id.* 12-13.

paid their KOL Volker Sonntag or of Medtronic's significant participation in the ghostwriting of the study.

675. Despite the two studies augmented by Medtronic's Vice President, the Senate Report cited studies that are in direct contrast with the Medtronic Defendants' initial publications. The Senate Report revealed that "spinal surgeons are beginning to question whether the "the oft-cited 'painful iliac crest donor site' is less serious and frequent than BMP enthusiasts would have us believe."[373]

676. A 2011 study included in the Senate Report found that "[t]he incidence of pain over the iliac crest was similar in patients in which iliac crest was harvested and those in which no graft was harvested." This study, and those like it, are in direct contrast with what is said in the Medtronic Defendants' sponsored studies and therefore not only cast serious doubt on the benefits of using BMP over traditional iliac crest bone graft, but the veracity of Medtronic in general.[374]

**3. Medtronic Arranged to Delete Adverse Events From Their Funded "Studies"**

677. The Senate Report found that "Medtronic employees not only edited the draft manuscript to include comments supportive of Infuse®, they also covertly participated in the peer-review process … on behalf of the physician authors named on the paper."[375]

678. Medtronic's KOL J. Kenneth Burkus, M.D. "sent a draft manuscript of the study to Medtronic officials asking for assistance with 'further data analysis.'"[376]

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[373] *Id.* at 11.
[374] *Id.* at 11, *citing* Hu, Serena S., *Commentary: Illiac crest bone graft: are the complications overrated? The Spine Journal*, June 2011, attached hereto as Exhibit 84 also *available at:* http://www.spine.org/Documents/TSJJune2011_Hu_Commentary.pdf; Howard *et. al., Posterior iliac crest pain after posterolateral fusion with or without iliac crest graft harvest, The Spine Journal, June 2011, available at* http://www.ncbi.nlm.nih.gov/pubmed/20947439 (also attached hereto as Exhibit 85).
[375] Exhibit 27 at 15.
[376] *Id.*

679. Bill Martin, Vice President for Spinal Marketing Global Communications, and Medical Education at Medtronic made it clear to other employees that the Medtronic Defendants "would play a '***supporting cast' in assisting Dr. Burkus.***"[377] (Emphasis added.)

**Sent:** Wednesday, January 01, 2003 8:06 AM
**To:** Beals, Neil; Wehrly, Peter [ITD Div. Pres.]
**Cc:** Bearcroft, Julie; Charlton, Clark; Martin, Bill; DeMane, Michael; Lipscomb, Bailey
**Subject:** RE: PLIF Study Manuscript

A word of caution.
I'm pretty sure that on this paper Dr. Burkus just wants us to provide him the data he requested. Dr. Burkus mentioned that his plan for this paper was to do all the work, put Drs Haid, Branch and Alexander's names first, and then he plans to route it to them "as is" for approval. If they don't agree with the data, then they may of course take their name off. Dr. Burkus has done ground work with Charlie and Reg and they have indicated initially that they seem to be fine with this - I don't anticipate any issues between them. Dr. Burkus wanted his name last (and all the neuro's first) so that it would be well accepted by the Neurosurgical community. I know that he has talked in depth with Charlie about what the paper *should*, and equally important, *should not* include.

A couple of additional thoughts:

680. The Medtronic Defendants' KOL, J. Kenneth Burkus, M.D. informed Bill Martin that he "***wanted his name last (and all the neuro's first) so that it would be well accepted by the Neurosurgical community***."[378] (Emphasis added.)

681. Vice-President Richard Treharne also instructed the Medtronic Defendants' KOL Steven Glassman, M.D. to dramatically downplay references to what he referred to as complications, related to Infuse® by stating in an email, "[a]gain it is probably too late, but page 14 line 13 says "The high complication rate is alarming and warrants intense scrutiny." I think what you are trying to say is that the occurrence adverse events (not effects as in the title) in these patients was higher than expected and warrants further investigation."[379]

[377] *Id.*
[378] Exhibit 27 at 15.
[379] *Id.* at 13-14.

682. Vice President Richard Treharne (recipient of the original FDA approval letter for Infuse® in 2002) wrote an email to Medtronic's KOL J. Kenneth Burkus, M.D. stating, "[i]n looking over the data, I was impressed with how well the BMP patients actually did. So much so that I added a few paragraphs at the end that you may not agree with."[380]

683. The additions to Medtronic's KOL J. Kenneth Burkus, M.D.' study by Vice President Richard Treharne read in part: "[i]n conclusion, this detailed, ***independent review*** of the results which represent the first of use osteoinductive proteins in a PLIF procedure are encouraging."[381] (Emphasis added.)

684. All of the above were unknown to *The Spine Journal*'s peer-review committee. However, following submission of the initial draft to *The Spine Journal*, the peer-reviewing physicians were critical of the article's "presentation of the study results." The bias added by Medtronic was so apparent that critiques by the peer-reviewers included: "***[u]nless the authors can discuss the results of this study in an unbiased manner, which they have not been able to do in its present form, this data should not be published***." Another reviewing physician stated, "***The manuscript is full of biased statements that are a reflection of the data evaluators-the company that markets the product…As it stands it is an advertisement for a specific product without significant scientific merit***."[382] (Emphasis added.)

685. In response to the concerns expressed by the peer-reviewing physicians, Medtronic's response "**seemingly misled *The Spine Journal***" according to the U.S. Senate Report. In response to a letter from one of *The Spine Journal's* peer-reviewers, the Medtronic Defendants assisted in a draft response noting, "[t]o help eliminate any potential bias, only one of the co-authors was a clinical investigator – the other three were independent reviewers of all

[380] *Id.* at 15.
[381] *Id.* at 16.
[382] *Id.*

the data. Since these data are taken from a clinical IDE study sponsored by a company, only the company would have all the data in its database – data that is reviewed by FDA auditors. We don't believe any discussion of bias is needed for the text."[383]

686. The U.S. Senate Report found that these "**independent reviewers**" - Medtronic's KOLs Regis Haid, M.D. and J. Kenneth Burkus, M.D. - received $7,793,000 and $722,000, respectively by the end of 2003 and a total of $31,930,150.79 by 2010.[384]

687. According to the Senate Report, the "draft letter, written at least in part by Medtronic on behalf of Dr. Burkus, did not disclose the company's role in directly editing the paper, nor did it disclose the magnitude of financial payments made to the supposed 'independent reviewers.'"[385]

688. The U.S. Senate Report also uncovered an email, between Medtronic's Senior Vice President and President for Europe, Canada, Latin America and Emerging Market, Michael Demane, to Medtronic's Vice President Bill Martin. Realizing that Medtronic's significant involvement in editing and ghostwriting had been uncovered, Demane stated, "this is going to hurt more than help because of the reviewers [sic] comments. Too late to turn back tho [sic]," in response to an upcoming editorial criticizing the study.[386]

689. Without shame or any sense of remorse or wrongdoing, the Medtronic Defendants defend their collaboration with physician authors in two ways; first, Medtronic claims that "[s]ome of the employees who reviewed these articles resided nominally in the "Marketing" Department, but the employees are technically and scientifically trained who have earned

[383] *Id.* at 17.
[384] *Id.* at 5.
[385] *Id.* at 17.
[386] *Id.*

doctoral or other advanced degrees in relevant disciplines and draw on deep expertise in the science of bone morphogenetic proteins."[387]

690. Second, Medtronic had the temerity to attempt to defend its practice ghostwriting journal articles by asserting that "[i]n every case, physicians—not Medtronic personnel—prepare draft manuscripts, select content, approve suggested modifications, and are responsible for the final article content that they submit for publication and review by the scientific community."[388]

691. However, the Medtronic Defendants paid authors such as their KOL "authors" J. Kenneth Burkus, M.D. and Volker Sonntag $6.38 million and $28.85 million, respectively, between 1998 and 2010 in the form of consultant fees, royalties, and other compensation.[389]

692. The Medtronic Defendants' KOL J. Kenneth Burkus, M.D. acting on behalf of Medtronic, co-authored 10 of the original 13 false studies.[390]

693. Both the Medtronic Defendants and the authoring physicians failed to disclose these financial relationships to the scientific community when they published these highly biased and now shown to be false "studies".

### R. YODA CONFIRMED THE CORRUPTION OF SCIENTIFIC INTEGRITY

694. Following the unprecedented findings by *The Spine Journal*, Medtronic, under its new CEO, Omar Ishrak, commissioned a subsequent review of the effectiveness of BMP and the integrity of their previously funded studies of Infuse®/BMP that had become the subject of significant controversy.

695. In August 2011, Medtronic provided a $2.5 million grant to Harlan Krumholz, M.D. to fund the Yale University Open Data Access Project (YODA).[391]

[387] *Id.* at 8.
[388] *Id.*
[389] *See id.* at 5.
[390] *See id.* at 6-7.

696. YODA's stated goal was to "increase transparency and enhance the public trust in industry-funded clinical trials by facilitating the independent assessment and dissemination of data relevant to the benefits and harms of drugs and devices."[392]

697. Through YODA, Yale led independent and systematic reviews conducted simultaneously by two (2) independent teams of the entire body of scientific evidence regarding the safety and effectiveness of Medtronic's recombinant bone morphogenetic protein-2 (rhBMP-2) product. Each team reviewed all of the data independently of each other.

698. In a public response to the initiation of the YODA study, twenty-one (21) preeminent spine surgeons voiced their concern about Medtronic's corruption of the independent study process. In an editorial, *A biologic without guidelines: the YODA project and the future of bone morphogenetic protient-2 research,* published in *The Spine Journal* in October 2012, the surgeons stated in part:

> [a]s a specialty, ***it is painful to consider how early prudent reporting of even the most obvious and suspicious adverse events might well have prevented a decade of serious complications*** related to the use of rhBMP-2. In retrospect, we can see how false confidence in a reportedly perfect safety profile promoted a period of BMP-2 application in areas of greater and greater potential danger. . . And yet, given the legacy of questionable research and limitations in the primary body of rhBMP-2 data, there is a possibility that expectations of YODA have been exaggerated.[393] (Emphasis added).

699. The editorial by these twenty-one (21) preeminent spine surgeons further noted that: "clinical researchers cannot act as financially engaged business associates, and dispassionate investigators cannot be both credible authors and entrepreneurs in research involving human subjects**…[m]any principal investigators in the Medtronic-sponsored trials**

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[391] Center for Outcomes Research & Evaluation (CORE), YODA Project, *available at* http://medicine.yale.edu/core/projects/yodap/index.aspx (also attached hereto as Exhibit 86).
[392] *Id.*
[393] Carragee EJ, *A biologic without guidelines: the YODA project and the future of bone morphogenetic protein-2 research,* 12 Spine J. 878, 877-80 (2012) (also attached hereto as Exhibit 87).

**had financial conflicts of unprecedented magnitude**, the effect of which will be difficult to estimate, but **nearly impossible to overestimate**, in post hoc analyses."[394] (Emphasis added).

700. Even Dr. Krumholz, the creator of YODA, when told of the findings in the U.S. Senate Report (October, 2012) and while the YODA studies were still in progress, expressed his concerns stating, "This sounds eerily familiar to many of the **transgressions** we've read about from the pharmaceutical industry…It paints a picture of a company very heavily involved in the science; **marketing contaminating the science**; and the medical profession and researchers being complicit."[395] (Emphasis added).

701. In hopes to quell concerns of further impropriety, two academic teams, Oregon Health and Science University and University of York, conducted an independent review, on behalf of YODA, with full access to all of Medtronic's clinical trials, post-marketing and safety data regarding rhBMP-2.[396]

702. Oregon Health and Science University stated that "[t]he primary aims of this report are 1) to estimate the effectiveness and harms of rhBMP-2 in spinal fusion in a systematic review using the individual patent data (IPD) when available, and 2) to assess reporting biases in published articles of industry-sponsored studies."[397]

703. Oregon Health and Science University released their findings in June of 2013 and found that: "**there was serious selective reporting and underreporting of adverse events in the published articles** for both rhBMP-2 and ICBG groups, especially in the Medtronic trials

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[394] *Id.* at 878-79
[395] *See*, Exhibit 23 at 2.
[396] rhBMP-2 Project, Center for Outcomes Research & Evaluation (CORE), YODA Project, *available at* http://medicine.yale.edu/core/projects/yodap/rhbmp/overview.aspx (also attached hereto as Exhibit 88).
[397] Rongwei Fu et al., *Effectiveness and Harms of Recombinant Human Bone Morphogenic Protein-2 (rhBMP-2) in Spine Fusion: A Systematic Review and Meta-analysis, Executive Summary,* Oregon Health & Science University, Executive Summary -1 (2013), pages cited attached hereto as Exhibit 89, complete document also *available at* http://medicine.yale.edu/core/projects/yodap/rhbmp/463_158786_OHSU rhBMP-2 Final Report.pdf.

published early. **The actual rates of adverse events were much higher than reported**."[398] (Emphasis added).

704. More specifically, the Oregon Health and Science University reported that the individual patient data (IPD) data contained "315 adverse events in the rhBMP-2 group and 274 adverse events in the autograft group two years after surgery."[399]

705. These findings are in direct contrast with the published version of the Medtronic-sponsored studies, which simply reported either "no unanticipated device-related adverse events" or "no adverse events directly or attributable to rhBMP-2."[400]

706. The Oregon-based study defined reporting bias as "…[the] incomplete or inaccurate reporting of study outcomes and encompasses publication bias, outcome reporting bias, multiple publication bias, location bias, language bias, time lag bias, citation bias, and others (e.g. ghostwriting, misrepresentation of facts, reframing)."[401]

707. After comparing results reported in the published literature to individual patient data, the authors concluded that "[e]vidence of reporting bias in the published articles of industry-sponsored trials is ***substantial.***"[402] (Emphasis added.)

708. Dr. Rongwei Fu, the lead author of the Oregon Health and Science University study, stated ***"[w]e found a lot of reporting bias*** *in [Medtronic's] published papers that tends to overstate the benefits and played down the risks*." Further, Dr. Fu said "***it was difficult to identify "clear indications" for using the product",*** *as Infuse® "'offered no additional benefits beyond the normal benefits' of the spine surgery*."[403] (Emphasis added).

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[398] *Id.* at Executive Summary -9.
[399] *Id.*
[400] *Id.; see also,* Exhibit 56 and Exhibit 65 at 473.
[401] Exhibit 89 at 10.
[402] *Id.* at Executive Summary -9.
[403] Christopher Weaver, *Studies Fail to Back Medtronic Spine Product*, The Wall Street Journal, (June 17, 2013), (attached hereto as Exhibit 90).

709. The misrepresentations and bias were not contained only to the "benefits" of BMP. The authors noted that some publications overemphasized "donor site hip pain," which was only assessed in the control group patients and only on the side of their ICBG.[404]

710. The authors recognized the consequences of this widespread reporting bias by stating "[s]uch underreporting and practice could affect the spine surgeons' ability to evaluate the balance between the benefits and harms of using rhBMP-2 and prevent informed consent."[405]

711. Following an independent review of Medtronic's data, Oregon Health and Science University study found that BMP had more adverse events and an increased risk associated with its use, when compared to the gold standard traditional ICBG.

712. Specifically, the YODA reviewers from Oregon found that BMP resulted in:

a. an overall risk of cancer almost triple that of ICBG;[406]

b. contrary to a previously published Medtronic-sponsored study, BMP does not have a higher rate of success in Posterolateral fusions;[407]

c. Subsidence occurred in four times as many patients using BMP in comparison to ICBG;[408]

d. a cohort study reported more aggressive resorption of the graft and endplates in the rhBMP-2 group compared with ICBG;[409]

e. 315 adverse events where found within studies in direct contrast to published results stating "no unanticipated device-related adverse events."[410]

713. Furthermore, a meta-analysis of the IPD showed that there was moderate strength of evidence of ***no consistent differences between rh-BMP-2 and ICBG in overall success and fusion***."[411] (Emphasis added).

[404] Exhibit 89 at Executive Summary -9.
[405] *Id.* at 84.
[406] *Id.* at Executive Summary -8 and at 81.
[407] *Id.* at Executive Summary -9.
[408] *Id.* at 30-31
[409] *Id.*
[410] *Id.* at Executive Summary -9.

714. This finding directly contradicts the false and misleading marketing materials provided by Medtronic directly to physicians and consumers on their websites which touted a greater fusion rates with BMP when compared to ICBG.

715. The Oregon Health and Science University concluded "[there was] substantial evidence of reporting bias, no evidence that rhBMP2 is more effective than ICGB in spinal fusion, and some evidence of an association with important harms."[412]

716. Further, Mark Helfand, MD, co-author of the report from Oregon Health & Science University discussed the results regarding Infuse® stating **"[i]t is hard to find a clear advantage for using it…When you add in the potential harms, it tips the scale further toward not using it."**[413] (Emphasis added.)

717. Similarly, YODA reviewers from the University of York, in York England stated that the three objectives of their independent review of Medtronic's data were to "1) [e]xamine the potential benefits of rhBMP-2; 2) Examine the potential harms of rhBMP-2; and 3) Assess the reliability of the published evidence base."[414]

718. University of York, in June of 2013, published results that were similar to those of Oregon Health and Science University. Their review found:

a. The use rhBMP-2 in spinal surgery had modest benefits when compared with ICBG surgery 24 months after surgery;[415]

b. a near doubling in number of cancers with rhBMP-2;[416]

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[411] *Id.* at Executive Summary -6.
[412] *Id.* at 86
[413] John Fauber, *Reports question benefit of Medtronic's spine* surgery product, (June 2013) *available at* http://www.jsonline.com/watchdog/watchdogreports/reports-question-benefit-of-medtronics-spine-surgery-product-b9935439z1-211874181.html (also attached hereto as Exhibit 91).
[414] Jennifer V.E. Brown et al., *Systemic review and meta-analysis of the safety and efficacy of recombinant human bone morphogenic protein-2 (rhBMP-2) for spinal fusion*, Centre for Reviews and Dissemination University of York, xiv-xv (2013), pages cited attached hereto as Exhibit 92; complete document also *available at* http://medicine.yale.edu/core/projects/yodap/rhbmp/463_158787_York rhBMP-2 Final Report.pdf.
[415] *Id.* at 49.

c. heterotopic bone growth was 5.57 times more likely to occur in PLIF and TLIF spinal fusions using BMP as opposed to ICBG;[417]

d. osteolysis or bone destruction was 4.26 times more likely to occur in a TLIF and 3.17 times more likely in PLIF using Infuse® than in a spinal fusion using ICBG;[418]

e. retrograde ejaculation was 4.76 times more likely with BMP than with ICBG;[419]

f. hardware failure was as high as 8.37 times more likely to occur using BMP than with ICBG with a comparator like the Maverick disc system;[420]

g. Analyses of adverse event IPD from the Medtronic-sponsored trials showed some adverse events to be more common among rhBMP-2 patients…Arthritis, implant-related events, retrograde ejaculation, adverse wound events and neurological, urogenital and vascular events were also more common among rhBMP-2 patients;[421] and finally,

h. University of York showed further concern stating, "[s]tudies published in the wider literature and post marketing data raise concerns about other adverse events not captured or easily apparent in the IPD provided, including heterotopic bone formation, osteolysis, retrograde ejaculation, urinary retention, and dysphagia. Owing to the non-randomised nature of the studies and difference between them, the strength of this body of evidence is weak and findings should be interpreted cautiously."[422]

719. University of York commented specifically on the reliability of Medtronic's published evidence stating, **"we found adverse events to be incompletely and inadequately described in the trial publications."**[423] (Emphasis added.)

720. Additionally, "comparing the CSR categories against the adverse events described in published journal articles suggests that ***adverse event reporting across the Medtronic publications is relatively sparse and inconsistent***."[424] (Emphasis added).

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[416] *Id.* at xvi.
[417] *Id.* at 75.
[418] *Id.* at 76.
[419] *Id.* at 81.
[420] *Id.* at 79.
[421] *Id.* at xvi.
[422] *Id.* at 119.
[423] *Id.* at xvi.

721. Further, University of York found that the ***"[p]ublished papers provided far less information than was available*** in the confidential CSRs (or in the supplied IPD). The way in which the adverse data were presented in the literature was ***highly inconsistent and the rationale for presenting some adverse events and not others was rarely clear***. Brief, vague statements in some publications that simply noted 'no unanticipated device-related adverse events' were inadequate and unhelpful. In our view, such statements, without supporting evidence, should not be considered acceptable for publication."[425](Emphasis added).

722. University of York stated further that ***"[s]tudies published in the wider literature and post marketing data raise concerns*** about other adverse events not captured or easily apparent in the IPD provided, including heterotopic bone formation, osteolysis, retrograde ejaculation, urinary retention, and dysphagia. Owing the non-randomised nature of the studies and difference between them, ***the strength of this body of evidence is weak and findings should be interpreted cautiously***."[426]

723. The main conclusion the University of York arrived at was that "rhBMP-2 seems to increase the chance of successful fusion, ***according to Medtronic definitions***, but this does not translate to clinically meaningful benefits in pain reduction, function or quality of life."[427] (Emphasis added).

724. The findings of the YODA reviewers did not go unnoticed. Medtronic manipulated the studies by creating a threshold definition of what constituted a fusion that is not accepted by the spine community but permitted Infuse® to have positive results in the "studies." Medtronic defined spinal fusion as a success or failure according to its own made-up definition.

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[424] *Id.* at 100.
[425] *Id.* at 118.
[426] *Id.* at xvi.
[427] *Id.* at 119.

Medtronic's definition allowed for "translation of less than or equal to 3 mm and angulation of less than 5 degrees."[428] The Mayo Clinic defines spinal fusion as "…surgery to permanently connect two or more vertebrae in your spine, eliminating motion between them".[429]

725. Other preeminent researchers and scientific journals also weighed in on the study results. Dr. Krumholz of Yale commented on the study findings stating that "***[e]vidence suggests that some data are not missing at random.***"[430] (Emphasis added.)

726. "Christine Laine, editor-in-chief of *Annals*, said it now will be difficult for doctors to recommend BMP-2 since it was shown to offer no meaningful benefit over the traditional method used for spinal fusion."[431] Dr. Laine's statement also further emasculates any claimed learned intermediary defense.

727. Further, "U.S. Senator Max Baucus, chairman of the Senate Committee on Finance, said the new reports amounted to more evidence of 'collusive relationships' between Medtronic and the doctors who wrote the questionable papers about Infuse. 'If not for those relationships and the misleading studies they produced, patients might have gotten more effective treatments and avoided harmful side effects,' Baucus said in a statement. 'The bottom line is ailing patients should never have to fear they're being sold a bill of goods.'"[432]

728. In its press release following the release of the YODA study results, *The Spine Journal* announced, ***"[i]n a triumph of understatement, the YODA group informs us that ten***

[428] Burkus JK, Gornet, MF, Dickman CA, Zdeblick TA, *Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages,* J. Spinal Disord. Tech, 2002; 15:337-39; (also attached hereto as Exhibit 27).
[429] Spinal Fusion, Mayo Clinic *available at* http://www.mayoclinic.com/health/spinal-fusion/my01235 (also attached hereto as Exhibit 93).
[430] As quoted in: Eugene Carragee, *Response to Long-Awaited YODA Report on Controversial Spinal Fusion Products,* The Spine Journal. (June 17, 2003), attached hereto as Exhibit 94; also *available at* http://www.spine.org/Documents/Carragee_Statement_YODA_Reports_061713.pdf.
[431] John Fauber, *Medtronic $$$ Buy Reports That Slam Spine Product,* (Jun 17, 2013), *available at* http://www.medpagetoday.com/PainManagement/BackPain/39903 (also attached hereto as Exhibit 95).
[432] *Id.*

***years after its development 'it is difficult to identify a clear indication for BMP-2 use in spinal fusion.'"***[433] (Emphasis added.)

729. Dr. Carragee, Chief Editor of *The Spine Journal* further explained in part:

> *To put the YODA finding in perspective, one must understand the carnival-like promotion that preceded BMP-2's fall from grace.* ***Market boosters advertised*** *that BMP-2 went beyond all other medical innovations. Perhaps confusing Infuse® with penicillin or the polio vaccine, one zealot proclaimed: '****Infuse, the single most successful biologic product ever launched in orthopedics and possibly ever in medicine****.'*
>
> *It is astonishing to recall the lavish praise for BMP-2 use by some Medtronic-associated surgeons just a few years ago****. . .Dr. Scott Boden declared, '[t]he age of BMP has arrived.'*** *Then within three months of FDA approval in July of 2002,* ***Dr. Thomas Zdeblich and Dr. J. Kenneth Burkus reported that Infuse had become their exclusive bone grafting method for anterior lumbar fusions:*** *"With it superiority,* ***InFuse Bone Graft may now become the new gold standard*** *for replacing autograft bone.*
>
> ***[A]n extraordinary merry-go-round of comprehensively conflicted faces are found where independent checks should have provided critical review.*** *In some instances, it seems the principal investigator with strong financial ties helped design a trial, and then acted as surgeons who monitored their own complications. To complete the circuit the same surgeon/investigator would co-author the paper and then submit the manuscript for review to…well…himself as chief or section editor of the journal. In some cases the editor in chief of the journal approving his own paper was also the developer and the royalty holder on products being investigated.*
>
> *And now the [Yale Open Data Access Project] group – echoing The Spine Journal's critical review from 2 years ago – tells us that important concerns about BMP-2 complications were 'underreported' or just missing. As YODA project director Harlan Krumholz, MD, SM, delicately puts it, '****Evidence suggests that some data are not missing at random****.' Annals editors are more blunt: '****Early journal publications misrepresented the effectiveness and harms through selective reporting, duplicate publication, and underreporting.' Ouch****.*[434]

730. Dr. Carragee concludes:

> ***[i]t's ultimately disappointing that after 15 years of largely self-congratulatory research, we have only indirectly discovered BMP-2' many potential***

[433] Exhibit 94.
[434] *Id.*

> ***complications…The suggested gap in our understanding if true, is simply appalling: these complications were systematically, 'misrepresented,' 'underreported' or just 'missing' from the first decade of publications.***[435] (Emphasis added).

731. However, Medtronic's reaction to the YODA results was, not surprisingly, misleading and disingenuous.

732. Following the release of the YODA studies, Omar Ishrak, CEO of Medtronic, publicly announcing as if YODA supported their methodology and past behavior, that over one million patients have used Infuse® and that the YODA study results "add to a growing body of evidence regarding INFUSE Bone Graft as a safe and effective treatment option for patients in approved indications for use."[436]

733. In making this public announcement, CEO Ishrak deliberately ignored the undisputed fact that over 85-90% of Infuse® surgeries were "off-label", as a result of Medtronic's illegal marketing, promotion, and distribution of Infuse®. Nor did CEO Ishrak disclose that YODA, the United States Senate, and independent leading experts in the spine community, severely criticized Medtronic for their actions and even questioned the use of Infuse® in light of the serious adverse risks with a lack of any increased benefit or advantage over other available techniques.

734. *The Journal of the American Medical Association* ("JAMA") published an article that appeared in the July 23, 2013 edition. JAMA is the most widely circulated medical journal in the world. The article addressed the YODA study. The title of the article accurately sums up the results: "Open Access to Data Closes the Book on Efficacy of Popular Bone-Graft Device."

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[435] *Id.*

[436] Press Release, Infuse Bone Graft Remains Important Treatment Option (June 17, 2013), *available at* http://newsroom.medtronic.com/phoenix.zhtml?c=251324&p=irol-newsArticle&id=1830515 (also attached hereto as Exhibit 96).

735. The article reports that YODA revealed Infuse® as product "has no clinical advantage over the traditional bone grafting methods." It further reports that both independent Universities found similar results, quoting York University's lead author Mark C. Simmonds; "[w]e think although we had different approaches, we did come up with similar findings [as the Oregon team]." The article reports that "[c]linically, Simmonds could not recommend using rhBMP-2." Finally, the Oregon Health and Science University study team noted "earlier release of all relevant data would have better-informed clinicians and patients making medical decisions."[437] The *JAMA* article is further recognition by the leaders of the medical community that Infuse® was misrepresented by Medtronic and its agent authors.

### S. BMP LEADS TO A FIVE-FOLD INCREASE IN CANCER

736. Doctors Eugene J. Carragee, Bradley K. Weiner, and other esteemed authors in the most recent study published in the September 4, 2013 edition of *The Journal Of Bone And Joint Surgery*, looking into the connection of rhBMP-2 and cancer, determined that the patients exposed to a 40 milligram dose of BMP experienced a 7.77% increase in risk of developing cancer in comparison to ICBG spinal fusions. When multiple cancers in a single patient were not considered, five-fold (5) more patients developed one or more cancers when compared to ICBG. Therefore, for every 17.4 patients, one patient developed cancer within two years of their spinal fusion using Medtronic's rhBMP-2. More specifically, rhBMP-2 may play a role in the tumor progression of pancreatic and breast cancer cells and the epithelial-to-mesenchymal, enabling the tumor to penetrate more deeply in lung cancer.[438]

[437] Mike Mitka, MSJ, *Open Access to Data Closes the Book on Efficacy of Popular Bone-Graft Device*, 359-340, (July 24, 2013) JAMA (also attached hereto as Exhibit 97).
[438] Eugene J. Carragee, et al., *Cancer Risk After Use of Recombinant Bone Morphogenetic Protein-2 for Spinal Arthrodesis*, The Journal of Bone and Joint Surgery 1537-1544, (July 2013) (also attached hereto as Exhibit 98).

737. Notably the population for this cancer study was selected based upon its low risk or likelihood for developing cancer from other external factors. The physician authors warn, "the cancer risk associated with rhBMP-2 may be greater in populations with a higher prevalence of indolent or in situ cancer (e.g., older individuals, those with a history of cancer or known concurrent cancer, and those with genetic or exposure-related predisposition)."[439]

## T. RECENT ISSUES OF THE SPINE JOURNAL DISCUSS CORRUPTED STUDIES

### 1. "Moving forward after YODA."

738. The September 2013 *The Spine Journal* editorial entitled "Moving forward after YODA", written by Eugene J. Carragee, M.D., Bradley K. Weiner, M.D., Eric L. Hurwitz, DC, Ph.D., and Mark L. Schoene, BS examined the safety concerns and the lessons learned of rhBMP-2.[440] In this article the authors stated the following in their conclusions:

- Our review discovered that rhBMP-2 appeared to work no better than iliac crest bone graph for fusion but that the potent growth factor did appear to have a number of potential drug- and implant-associated adverse events, including some very serious complications.

- The YODA findings confirmed the *TSJ* findings and, indeed, identified several additional research problems *including the apparent misrepresentation of effectiveness and safety in the early articles through selective and incomplete reporting and the fact that the research design limited the ability of the studies to precisely assess safety. They concluded that 'rhBMP-2 provided little or no benefit compared to bone graft and may be associated with more harms, possibly including cancer.'* (Emphasis added).

- [W]e note that some of the YODA and the *Annals* editors suggest that there may be *no clear* indications for use.

- The YODA findings suggest that the entire research system, at least for commercial products, has broken down in a fundamental way and needs to be redesigned.

[439] *Id.*
[440] Eugene J. Carragee, et al., *Moving forward after Yoda,* The Spine Journal 995 -997 (September 2013) (also attached hereto as Exhibit 99).

- It provides the clearest argument for reform of the current system and open access to data, to protect the health and safety of patients, and the ability of health-care providers to provide humane and effective treatment. *The BMP-2 issue is just the most recent example (eg Vioxx, Tamiflu, Paxil, Avandia) to show that questionable behavior has been going on in the medical research for years, resulting in publication/reporting bias, biased systematic reviews, and public health and patient harm."* (Emphasis added).

- For all: Really, it is about putting patient safety ahead of personal financial profit, professionalism pride/ego, and surgical convenience.

### *2. The Spine Journal* "When Money Talks"

739. The September 2013 issue of *The Spine Journal*, has an article written by David J. Rothman, PhD and Sheila M. Rothman, PhD entitled "When money talks."[441] In the article the authors concluded the following:

- Despite the explicit and detailed reports of extensive financial ties between physicians and researchers on the one hand and device and drug companies on the other hand… some recipients of industry largess continue to deny that these relationships are in any way problematic.

- *One outstanding case in point involves Medtronic-funded studies on BMP-2, as examined in 2011 in this journal.* As many readers will know, critics found the results of the Medtronic studies so self-serving and incomplete that the company funded and released all its BMP-2 research data to the Yale University Open Data Access Project. (Emphasis added).

- In June 2013, the findings of two independent research teams were published, and one of them (Fu et al.) was particularly troubled by the effects of company-sponsored research. 'No trials were truly independent of industry sponsorship,' its author concluded. 'Earlier disclosure of all relevant data would have better informed clinicians and the public then the initial published trial reports did' [9]. So too, the editors of the Annals of Internal Medicine concluded that '*Early journal publications misrepresented the effectiveness and harms through selective reporting, duplicate publication and underreporting*.' In other words, just as gifts bias the recipient, so apparently do research grants and consulting [10]. (Emphasis added).

- In most cases, recipients of company largess are not being 'bribed'—they are being 'gifted.'

[441] David J. Rothman, et al. *When Money Talks*, The Spine Journal 998-1000 (September 2013) (also attached hereto as Exhibit 100).

- The Yale University Open Data Access Project groups critical assessment of decade-old research was not only relevant to the company but also reflected back in stark terms on the original authors…

- *Patient welfare and scientific integrity are too important to allow bias to affect the research reports in journal articles, the prescribing habits of physicians, the content of lectures, the decisions of professional associations' guideline committees, and the choice made by formularies for drugs and devices.* (Emphasis added).

- Those denying or qualifying the reality and scope of the problem are in a losing position. To be sure, scandals will inevitably recur. The drive for income and profit, no matter what the cost, cannot be completely contained.

**3. *The Spine Journal* "Black, white, or gray: how different (or similar) are YODA and the Spine Journal reviews of BMP-2?"**

740. In the September 2013 issue of *The Spine Journal* an NASS review article written by Christopher M. Bono, M.D., F. Todd Wetzel, M.D., on behalf of the North American Spine Society Executive Committee, endorsed by the North American Spine Society Section on Biologics entitled "Black, white, or gray: how different (or similar) are YODA and the Spine Journal reviews of BMP-2?" examined the outcomes and adverse events of BMP-2 comparing the studies and data used from the Yale University YODA study and the Spine Journal 2011study.[442]

741. The publications reviewed were: (a) The 2011 The Spine Journal article by Dr. Carragee et al. entitled "A critical review of recombinant human bone morphogenetic protein-2 trials in spinal surgery: emerging safety concerns and lessons learned"; (b) The YODA article by Dr. Simmonds et al. entitled "Safety and effectiveness of recombinant human bone morphogenetic protein-2 for spinal fusion"; and (c) The article by Dr. Fu et al. entitled

[442] Christopher M. Bono, et al., *Black, white, or gray: how different (or similar) are YODA and the Spine Journal reviews of BMP-2*, The Spine Journal 1001-1005 (also attached hereto as Exhibit 101).

"Effectiveness and harms of recombinant human bone morphogenetic protein-2 in spine fusion".[443]

742. The authors reviewed the original Dr. Carragee studies because Dr. Carragee "concluded that 'Level I and Level II evidence from *original FDA summaries, original published data, and subsequent studies suggest possible study design bias in the original trials, as well as a clear increased risk of complications and adverse events to patients receiving rhBMP-2 in spinal fusion.*' Furthermore, they documented that the '*risk of adverse events associated with rhBMP-2 is 10 to 50 times the original estimates reported in the industry-sponsored peer reviewed publications.*'"[444] (Emphasis added.)

743. In this recent article comparing the results of the Carragee studies with the YODA publications, the authors concluded that Carragee's original review was correct and was further corroborated by the YODA findings. They stated:

> With careful examination of these findings, it appears that the concern of Carragee et al. [2] about leg pain in the early postoperative after surgery is substantiated by both reviews. Regarding cancer risk, Fu et al. [5] found a stronger association than both Caragee et al. [2] and Simmonds et al… [445]

744. The authors went on to say:

> Simmonds et al. [3] appear to be in agreement with Carragee et al. [2] regarding concerns of retrograde ejaculation, urogenital complications, subsidence, infections, and implant-related adverse events (if this can be used as a proxy for osteolysis). Fu et al. [5] seem to corroborate these concerns, finding that retrograde ejaculation, subsidence, and urogenital problems were more common with BMP…
>
> The common conclusion of the three groups was that heterotopic (i.e., ectopic) bone formation was much more common with rhBMP-2... [446]

[443] *Id.* at 1001.
[444] *Id.*
[445] *Id.* at 1003.
[446] *Id.* at 1004.

745. Finally, the authors said, "Suffice it to say that Fu et al. [5], similar to Carragee et al. [2], found instances in which 'no adverse events because of rhBMP-2' were reported when in fact IPD analysis found that they in fact did occur (and were recorded)."[447]

### U. MEDTRONIC'S COVER UP OF ADVERSE EVENTS AND INCREASED RISKS CAUSED PLAINTIFFS' INJURIES.

746. A manufacturer has the duty to provide adequate and timely warnings regarding increased risks and dangers associated with the foreseeable uses of its product.

747. Medtronic knew that BMP was being widely used for non-approved uses, in non-approved ways, by untrained surgeons and in violation of federal law and the restrictions set forth in the PMA.

748. Medtronic knew that Class II cages (including P's cages and cages manufactured by other entities) were being widely used for non-approved uses, in non-approved ways, in violation of federal law and the restrictions set forth in the PMA.

749. Medtronic actively encouraged such use through its illegal promotional scheme and other illegal activities.

750. Medtronic grossly failed to satisfy its duty mandated by federal law, the PMA, and state common law duties.

751. Medtronic did not provide adequate and timely warnings or instructions regarding the "off-label" uses of Infuse®, its components and P's cages.

752. Medtronic directed/encouraged and helped to disseminate misleading and false information concerning the "off-label" use of Infuse®, its components and P's cages.

753. Medtronic provided undisclosed financial incentives to lecturing physicians, authors of scientific and medical articles, and sales representatives.

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[447] *Id.*

754. Medtronic purposefully concealed the serious increased risks and complications associated with "off-label" use of Infuse® and its components.

755. **Medtronic failed to take the required action when it learned that the BMP/Sponge component and P's cages were being used in ways and in a manner that was not approved and required by the PMA**, all of which is in direct violation of federal law and the PMA.

756. Medtronic cannot and should not be permitted to absolve itself from liability by pointing to the "off-label" use of its device by physicians or by pointing to the FDCA or the MDA, claiming preemption, when it is Medtronic who chose to violate the law by deliberately concealing its knowledge of the increased risks, complications, and the serious and dangerous adverse side effects associated with "off-label" use of BMP.

757. Medtronic cannot and should not be permitted to absolve itself from liability by pointing to the off-label use of its device by physicians, when it is Medtronic who, in violation of federal law and the PMA, distorted the actual facts of the studies so as to conceal the true adverse events observed with the use of BMP as compared to that of other types of procedures and techniques, all while concealing Medtronic's involvement in that scheme.

758. A medical device manufacturer only gets the benefits afforded by federal law, *i.e.* the FDCA and MDA, when it abides by federal law.

759. Federal law requires that a medical device manufacturer submit to the FDA a premarket application for approval of a Class III medical device, including proposed labeling, setting forth the proposed "intended uses" of the medical device.

760. It is only the "intended uses" set forth by the device manufacturer in the premarket application that the FDA put through the premarket approval review process and ultimately passes on.

761. If a medical device manufacturer markets, promotes, distributes and/or sells a medical device for uses other than the "intended use" that went through the FDA premarket approval process, those unapproved and un-reviewed uses are not afforded any of the benefits of federal law including the FDCA and MDA.

762. Medtronic's aggressive marketing efforts influenced Plaintiffs' physicians to use BMP and P's cages in an "off-label" and unapproved, expreimental manner.

763. The degree to which Medtronic secretly promoted "off-label" BMP was so permanent and pervasive that "off-label" use in fact represented nearly 90% of all Infuse® sales.

764. Medtronic's illegal promotion of BMP for "off-label" use and its concealment of material information regarding the risks associated with "off-label" use of BMP was therefore the proximate cause of Plaintiffs' injuries.

765. Not only did Medtronic not provide the Plaintiffs' physicians or Plaintiffs with the necessary information in order to make an informed decision in the best interests of Plaintiffs' health, Medtronic intentionally and purposefully deceived Plaintiffs' physicians and Plaintiffs as to the safety and efficacy of BMP.

766. Medtronic did not discharge its duty, required by federal law, the PMA, and state common law, to adequately and fully warn and inform Plaintiffs' physicians and Plaintiffs of the known dangers and increased risks associated with the "off-label" and unapproved use of BMP nor did Medtronic provide Plaintiffs' physicians with adequate instructions for its use.

767. Plaintiffs' physicians and Plaintiffs reasonably relied, and did rely, on Defendants' misrepresentations and concealments.

768. Moreover, Plaintiffs would not have consented to the "off-label" and unapproved use of Infuse® or any of its components had Plaintiffs been fully informed of its increased dangers, risks, and adverse consequence.

769. As a direct and proximate result of Medtronic's fraudulent concealment and misrepresentations concerning material health and safety risks related to BMP, as well as Medtronic's reckless and irresponsible "off-label" promotion and marketing practices, Plaintiffs were permanently injured and suffered and will continue to suffer injuries, damages, and economic loss.

770. As the direct, proximate and legal result of Medtronic's fraudulent concealment and misrepresentations concerning material health and safety risks related to BMP, as well as Medtronic's reckless and irresponsible "off-label" promotion and marketing practices, Plaintiffs have been injured and have incurred damages, including but not limited to medical and hospital expenses, physical and mental pain and suffering, and loss of the quality and enjoyment of life as a result.

## V. EQUITABLE TOLLING/FRAUDULENT CONCEALMENT.

771. Plaintiffs repeat and incorporate by reference all other paragraphs of this Complaint as if fully set forth herein and further allege as follows:

772. Medtronic's failure to document or follow up on the known defects of its products, and concealment of known defects, serious increased risks, dangers, and complications, constitutes fraudulent concealment that equitably tolls any proffered statute of limitation that may otherwise bar the recovery sought by Plaintiffs herein.

773. The Medtronic Defendants named herein are estopped from relying on any statute of limitations defense because they continued to refute and deny reports and studies questioning the safety of BMP, actively and intentionally concealed the defects, suppressed reports and adverse information, crafted the published reports to falsely increase the benefits of BMP while falsely increase the adverse event profile of the alternative procedures and methods, failed to satisfy FDA and PMA requirements, failed to satisfy FDA and PMA notification requirements, and failed to disclose known dangerous defects and serious increased risks and complications to physicians and the Plaintiffs.

774. Instead, the Medtronic Defendants continued to represent BMP was/is safer, more effective and the best alternative for spinal fusion all the while they knew that this was absolutely false and not true, even after the United States Senate report and the YODA study were released.

775. The Medtronic Defendants did the above acts which were and are illegal under federal law, the PMA, and parallel state law, to encourage surgeons to use Infuse® and its components in "off-label" manners.

776. The Medtronic Defendants named herein did the above acts which were and are illegal under federal law, the PMA, and parallel state law, to encourage patients to permit their surgeons to use Infuse® its components in "off-label" manners.

777. At all relevant times, the Medtronic Defendants were under a continuing duty under federal law, the PMA, and parallel state laws to disclose the true character, quality, and nature of the increased risks and dangers associated with Infuse®.

778. As a result of the Medtronic Defendants' concealment of the true character, quality and nature of their products, they are estopped from relying on any statute of limitations defense.

779. The Medtronic Defendants furthered their fraudulent concealment through acts and omissions, including misrepresenting known dangers and/or defects in the BMP/Sponge and P's Cages and/or arising out of the use of the BMP/Sponge and P's Cages, and a continued and systematic failure to disclose and/or cover-up such information from/to the Plaintiffs, Plaintiffs' physicians, and the public.

780. The Medtronic Defendants' acts and omissions, before, during and/or after the act causing Plaintiffs' injuries, prevented Plaintiffs and/or Plaintiffs' physicians from discovering the injury or cause thereof until recently.

781. The Medtronic Defendants' conduct, because it was purposely committed, was known or should have been known by them to be dangerous, heedless, reckless, and without regard to the consequences or the rights and safety of the Plaintiffs.

## VI. GENERAL ALLEGATIONS

782. Plaintiffs repeat and incorporate by reference all other paragraphs of this Complaint as if fully set forth herein and further allege as follows:

783. At all relevant times, the BMP/Sponge was researched, developed, manufactured, marketed, promoted, advertised, sold, designed and/or distributed by the Medtronic Defendants.

784. At all relevant times, the vast majority of P's Cages were developed, manufactured, marketed, promoted, advertised, sold, designed and/or distributed by the Medtronic Defendants.

785. The Medtronic Defendants negligently, carelessly, and/or recklessly manufactured, marketed, advertised, promoted, sold, designed and/or distributed the BMP/Sponge and/or P's Cages as safe and effective devices to be used for posterior spinal fusion surgery.

786. The Medtronic Defendants knew, and/or had reason to know, that the BMP/Sponge and P's Cages were defective, unreasonably dangerous, and not safe for the purposes and uses that these Defendants intended.

787. The Medtronic Defendants knew, and/or had reason to know, that the BMP/Sponge and P's Cages were defective, unreasonably dangerous and not safe for FDA non-approved uses because the adverse events reported and scientific studies performed showed substantially increased risks of serious dangers.

**Representations**

788. The Medtronic Defendants promoted the BMP/Sponge and P's Cages for surgeries that are outside of the intended uses for these devices approved by the FDA.

789. The Medtronic Defendants negligently, carelessly, recklessly, and/or intentionally promoted the BMP/Sponge and P's Cages for purposes outside of the intended uses approved by the FDA to physicians and patients, including the Plaintiffs herein and Plaintiffs' physicians.

790. The Medtronic Defendants downplayed to physicians and patients, including Plaintiffs herein and Plaintiffs' physicians the dangerous side effects of using the BMP/Sponge in combination with P's Cages, including downplaying the dangers of FDA-approved devices and uses.

791. The Medtronic Defendants misrepresented the safety of the BMP/Sponge in combination with P's Cages to physicians and patients, including Plaintiffs and Plaintiffs' physicians.

792. The Medtronic Defendants willfully and/or intentionally failed to warn and/or alert physicians and patients, including Plaintiffs and Plaintiffs' physicians, of the increased risks

and significant dangers resulting from the FDA-unapproved use of the BMP/Sponge in combination with P's Cages.

793. The Medtronic Defendants knew and/or had reason to know, that their representations and suggestions to physicians that the BMP/Sponge in combination with P's Cages were safe and effective for such uses, were materially false and misleading and that physicians and patients including Plaintiffs and Plaintiffs' physicians, would rely on such representations.

794. The Medtronic Defendants and their agents knew or should have known and/or recklessly disregarded the materially incomplete, false, and misleading nature of the information that they caused to be disseminated to the public and to physicians, including Plaintiffs and Plaintiffs' physicians, as part of Medtronic's surreptitious campaign to promote the BMP/Sponge in combination with P's Cages for use outside of their intended uses approved by the FDA and thus unapproved and experimental.

795. Any warnings the Medtronic Defendants may have issued concerning the dangers of using these devices outside the intended uses approved by the FDA of Infuse® or regarding the specific risks of those uses were inadequate and insufficient in light of Medtronic's contradictory prior, contemporaneous and continuing illegal promotional efforts and over-promotion of the BMP/Sponge and/or P's Cages for non-FDA-approved uses in the spine and contemporaneous efforts to hide or downplay the true increased risks and serious dangers of such unapproved uses.

796. The ongoing scheme described herein could not have been perpetrated over a substantial period of time, as has occurred here, without knowledge and complicity of personnel at the highest level of the Medtronic Defendants, including the corporate officers.

797. The Medtronic Defendants knew and/or had reason to know of the likelihood of serious injuries caused by the off-label use of the BMP/Sponge in combination with P's Cages, but they concealed this information and did not warn Plaintiffs or Plaintiffs' physicians, preventing Plaintiffs and Plaintiffs' physicians from making informed choices in selecting other treatments or therapies prior to Plaintiffs' implantation surgery and preventing Plaintiffs and Plaintiffs' physicians from timely discovering Plaintiffs' injuries.

798. Had the Medtronic Defendants performed adequate clinical and preclinical testing of the BMP/Sponge and P's Cages in combination with biologics, these defendants would have discovered that P's Cages were not adequately designed for use with a biologic. These Defendant knew or should have known about the inadequacy of the design of a "system" of administration of the biologic, BMP, via just the BMP/Sponge alone or with P's Cages. These Defendants had parallel duties, under state and federal law, to perform such testing and then warn against the use of P's Cages with a biologic, detailing in such warning the risk and benefit information that eventually became public in the YODA study and the June, 2011 issue of The Spine Journal.

**Causation**

799. Plaintiffs would not have consented to be treated with the BMP/Sponge and/or P's Cages had Plaintiffs known of or been fully and adequately informed by the Medtronic Defendants of the true increased risks and serious dangers of using these devices together, which created a new device, untested by adequate clinical trials and experimental and thus, unreasonably dangerous.

800. Plaintiffs and Plaintiffs' physicians reasonably relied on Medtronic's representations and omissions regarding the safety and efficacy of Medtronic's medical devices in Plaintiffs' spine surgeries.

801. Plaintiffs and Plaintiffs' physicians did not know of the specific increased risks and serious dangers, and/or were misled by the Medtronic Defendants, who knew or should have known of the true risks and dangers, but consciously chose not to inform Plaintiffs or Plaintiffs' spine surgeons of those risks and to actively misrepresent those risks and dangers to the Plaintiffs and Plaintiffs' physicians.

802. The Medtronic Defendants' promotion and marketing of the BMP/Sponge, either alone or in combination with P's Cages, caused Plaintiffs' surgeons and/or Plaintiffs to decide to implant these devices in Plaintiffs using them for purposes outside FDA-approved uses..

**Damages**

803. Plaintiffs have suffered serious personal injuries as a direct and proximate result of the Medtronic Defendants' misconduct.

804. As a direct and proximate result of the these Defendants' wrongful conduct and the use of these defendant's defective devices in these surgeries, Plaintiffs have suffered and will continue to suffer from severe injuries and damages, including but not limited to severe pain, great emotional distress, and mental anguish.

805. As a result of the off-label use and failure to warn of the risks associated with the off-label use of the BMP/Sponge and/or P's Cages as manufactured, promoted, sold and/or supplied by the Medtronic Defendants, and as a result of the negligence, callousness and the other wrongdoing and misconduct of the Medtronic Defendants as described herein:

a. Plaintiffs have been injured and suffered injuries to their bodies and minds, the exact nature of which are not completely known to date;

b. Plaintiffs have sustained economic losses, including loss of earnings and diminution of the loss of earning capacity, the exact amount of which is presently unknown;

c. Plaintiffs have incurred medical expenses and will be required to incur additional medical expenses in the future to care for themselves as a result of the injuries and damages Plaintiffs have suffered;

d. Plaintiffs are therefore entitled to damages in an amount to be proven at trial, together with interests thereon and costs.

806. Plaintiffs had no reason until recently to suspect that their chronic pain and injuries were caused by Defendants' defective and unreasonably dangerous medical devices. Plaintiffs did not know and could not have known and through the exercise of reasonable diligence could not have known that the use of the BMP/Sponge alone, and/or in combination with P's Cages, caused their injuries. For these reasons, Plaintiffs' Complaints were all filed within the time period allowed by the applicable statutes of limitations.

807. The Plaintiffs herein bring this action within the applicable statutes of limitations. Specifically, Plaintiffs bring this action within the prescribed time limits following their injuries and their knowledge of the wrongful cause. Prior to such time, Plaintiffs did not know nor had reason to know of their injuries and/or the wrongful cause thereof.

## VII. VIOLATIONS OF FEDERAL LAW PARALLEL STATE CAUSES OF ACTION.

808. Plaintiffs repeat and incorporate by reference all other paragraphs of this Complaint as if fully set forth herein and further allege as follows:

809. The Medtronic Defendants falsely represented the results of scientific studies regarding BMP and Infuse®.

810. The Medtronic Defendants concealed material information related to the safety of FDA-unapproved use of Infuse® and its components.

811. The Medtronic Defendants covertly edited scientific studies to falsely enhance the purported benefits of BMP.

812. The Medtronic Defendants deceptively and falsely underreported the dangerous propensities and increased risks of BMP.

813. The BMP component of Infuse® that was implanted in Plaintiffs was promoted, distributed, and used in an FDA unapproved manner that is in violation of federal law, including the FDCA, MDA and regulations related thereto, as well as parallel state laws.

814. P's Cages that were implanted in Plaintiffs were promoted, distributed, and used in an FDA-unapproved manner that is in violation of federal law, including the FDCA, MDA, and regulations related thereto, as well as parallel state laws.

815. Plaintiffs were injured due to the FDA-unapproved and/or "off-label" use of a component of Infuse® that resulted from the Medtronic Defendants' practice of promoting such uses. By engaging in such promotion, the Medtronic Defendants caused the components and parts of Infuse® as distributed to be misbranded.

816. Advertising or promoting Infuse® "in a manner that is inconsistent with any conditions to approval specified in the PMA approval order for the device," renders the medical device "misbranded."

817. The Medtronic Defendants violated federal law by engaging in such promotion that damaged Plaintiffs. This promotion misbranded the components of Infuse® that were promoted by these Defendants and were separate and distinct devices from Infuse®.

818. It was the duty of the Medtronic Defendants to comply with federal law, the FDCA, the MDA, the regulations and all state common law duties. Notwithstanding this duty,

the Medtronic Defendants violated federal law, the FDCA, the MDA, and the regulations, including but not limited to the regulations listed below:

a. **21 C.F.R. § 801.4j** because a Medtronic sales representative, acting on behalf of the Medtronic Defendants, was present in the operating room during many of Plaintiffs' procedures, knowing that Plaintiffs' Surgeons were using components of Infuse® without adequate labeling, approved by the FDA.

b. **21 U.S.C. § 360e** because the Medtronic Defendants failed to submit a PMA Application for the intended uses of BMP that they promoted "off-label" and/or as a device, in combination with other devices, that as a regulatory matter were distinct and different than the Infuse® "system" approved by the FDA.

c. **21 C.F.R. § 814.39** because the Medtronic Defendants failed to submit a PMA or a Supplement for uses of the components of Infuse® clearly shown through their "objective" intent.

d. **21 C.F.R. § 888.3080** because the Medtronic Defendants failed to obtain premarket approval for the use of BMP with cages other than the L-T Cage.

e. **21 U.S.C. § 352(b)** because the Medtronic Defendants promoted for sale misbranded and adulterated products, which were the separate components of Infuse®.

f. **21 U.S.C. § 331(a)** because the Medtronic Defendants introduced into interstate commerce a medical device (the "BMP" component of Infuse®) that was misbranded.

g. **21 U.S.C. § 331(k)** because the Medtronic Defendants altered the advertising and promotional material for Infuse® while its components were being held for sale after shipment in interstate commerce that results in the device being misbranded.

h. **21 C.F.R. § 801.5** because the Medtronic Defendants failed to provide adequate directions for the unapproved off-label uses of the components of Infuse® which they promoted and distributed separately.

i. **21 U.S.C. § 352(q)** because the Medtronic Defendants created and distributed false and misleading advertising for Infuse®, which is a "Restricted Device."

j. **21 C.F.R. § 801.4** because the Medtronic Defendants promoted new "off-label" and unapproved uses as reflected by their objective intent.

k. **Fed. Reg. 14286 (Mar. 16, 2000)** because the Medtronic Defendants distributed a product for a use that the FDA has not approved as safe and effective.

l. **21 C.F.R. § 801.4** because the Medtronic Defendants did not provide adequate directions and warnings after they had notice and knowledge that Infuse® components were being used for purposes other than the ones for which the device had been approved.

m. **21 C.F.R. § 820.3(z)(x), 21 C.F.R. § 820.22, 21 C.F.R. § 820.5, 21 C.F.R. § 820.1(a), 21 C.F.R. § 820.22, 21 C.F.R. § 820.160(a), 21 C.F.R. § 820.198(a) and 21 C.F.R. § 820.170(a)** because the Medtronic Defendants failed to comply the general quality control standards found in these regulations.

n. **21 C.F.R. § 814.80, 21 C.F.R. § 803.50(a), and 21 U.S.C. § 360i(a),** because the Medtronic Defendants failed to timely report adverse events.

o. **21 C.F.R. § 814.84(b)(2)** because the Medtronic Defendants failed to report new clinical investigations or scientific studies concerning BMP and/or Infuse® about which Medtronic knew or reasonably should have known.

p. **21 U.S.C. §§ 360(q); 360(r)** because the Medtronic Defendants created and distributed false and misleading advertising.

q. **21 U.S.C. § 360aaa and 21 U.S.C. § 360aaa-1** because the Medtronic Defendants' conduct far exceeded the limitations of the safe harbor provisions of providing copies of peer reviewed scientific articles to physicians between 1997 and 2006.

r. **21 C.F.R. § 820.198** because the Medtronic Defendants failed to establish and maintain procedures for implementing corrective and preventative action in response to, *inter alia*, complaints regarding Infuse®, and other quality problems associated with the Infuse®.

s. **21 C.F.R. § 820.198 and 21 C.F.R. § 803.3** because the Medtronic Defendants failed to appropriately respond to adverse incident reports that strongly indicated the Infuse® was malfunctioning or otherwise not responding to its Design Objective Intent.

t. **21 C.F.R. § 820.198 and 21 C.F.R. § 803.3** because the Medtronic Defendants continued to sell Infuse® into the stream of interstate

commerce when they knew, or should have known, that Infuse® was malfunctioning or otherwise not responding to its Design Objective Intent.

u. **21 C.F.R. § 814.80** because Infuse® was manufactured, packaged, stored, labeled, distributed, and/or advertised in a manner that is inconsistent with the conditions for approval specified in the PMA approval for it.

v. **21 C.F.R. § 801.109(c)** because the labeling for Infuse®, including the purposes for which it is advertised or represented, were outside of the intended uses approved by the FDA.

w. **21 C.F.R. § 801.6,** rendering Infuse® misbranded, because the representations Medtronic made in the labeling (including its advertising) were false and/or misleading with respect to non-approved uses.

x. **21 C.F.R. § 820.30(g)** because the Medtronic Defendants failed to test the misbranded and adulterated products, which were the separate components of Infuse® combined with other Class II cages, in actual or simulated use conditions.

819. As a direct and proximate result of Medtronic violations of one or more of these federal statutory and regulatory standards of care, a component of Infuse® was implanted in Plaintiffs and caused them to endure a serious injuries, as defined in 21 C.F.R. § 803.3. Plaintiffs were caused to suffer, and will suffer in the future, injuries including, but not limited to pain, suffering, lost wages, disability, disfigurement, legal obligations for hospital, medical, nursing, rehabilitative, and other medical services and treatment. All of these injuries are permanent.

820. The Medtronic Defendants failed to act as a reasonably prudent medical device manufacturer, distributor, and/or promoter in violating the FDCA, the MDA and the above-listed FDA Regulations. While violations of these specific statutes and regulations is detailed above, Plaintiffs are not asserting any cause of action for negligence per se, but instead are only asserting those state law causes of action enunciated below.

821. To be sure, Plaintiffs are not seeking to enforce these provisions in this action. Likewise, Plaintiffs are not suing merely because the Medtronic Defendants violated these provisions. Rather Plaintiffs are alleging that Medtronic Defendants' conduct that violated these provisions also violated parallel state laws and are pleading these violations of federal law solely in anticipation that the Medtronic Defendants will assert their affirmative defense of federal preemption.

822. The Medtronic Defendants' violations of the aforementioned federal statutes and regulations establish a *prima facie* case of liability under state common law, as expressed below.

823. Thus, in violating of federal law, including the FDCA, the MDA, and regulations promulgated thereunder, there exist causes of action under state common law for money damages, expressed below.

## VIII. AGENCY, ALTER-EGO, JOINT VENTURE, AND CONSPIRACY

824. At all times herein mentioned, each of the Defendants was the agent, servant, partner, aider and abettor, and/or co-conspirator of each of the other Defendants herein and/or engaged in a joint venture with each of the other Defendants herein.

825. At all times herein mentioned, each Defendant was operating and acting within the purpose and scope of said agency, service, employment, partnership, conspiracy and/or joint venture and rendered substantial assistance and encouragement to the other Defendants while knowing their collective and individual conduct constituted a breach of duty owed to the Plaintiffs.

826. At all times herein mentioned, the Defendants were fully informed of the actions of their agents, representatives, contractors, and/or employees, including but not limited to KOLs, and thereafter, no officer, director or managing agent of the Defendants repudiated those

actions. The failure to repudiate constituted adoption and approval of said actions, and all Defendants and each of them thereby ratified those actions.

827. At all times mentioned herein, there existed (and still exists) a unity of interest between certain Defendants and other certain Defendants such that any individuality and separateness between the certain Defendants has ceased, and these Defendants are the alter-egos of the other certain Defendants and exerted control over those Defendants. Adherence to the fiction of the separate existence of these certain Defendants as entities distinct from other certain Defendants will permit an abuse of the corporate privilege, sanction a fraud, and/or promote injustice.

828. Each of the Defendants herein expressly or impliedly agreed to work with and assist each other Defendant and unnamed parties, including but not limited to KOLs, toward the common purpose of the off-label promotion and usage of BMP and P's Cages and toward the common interest of pecuniary gain.

829. Each of the Defendants herein performed the acts and omissions described herein in concert with the other Defendants herein and/or pursuant to a common design with the other Defendants herein.

830. Each of the Defendants herein knew the acts and omissions of the other Defendants herein and their KOLs constituted a breach of duty, and yet, each Defendant herein provided each other Defendant substantial assistance and/or encouragement.

831. Each of the Defendants herein provided substantial assistance to the other Defendants herein in accomplishing the intentional and tortious conduct described herein, and each Defendants' conduct, even when separately considered, constitutes a breach of duties owed to the Plaintiffs.

832. At all times herein mentioned, each of the Medtronic Defendants were engaged in the business of and/or were a successor in interest to and/or affiliated with/associated with/indistinguishable from entities engaged in the business of researching, designing, formulating, compounding, testing, manufacturing, producing, processing, assembling, inspecting, distributing, marketing, labeling, promoting, packaging, prescribing, advertising for sale, and/or selling the BMP/Sponge and P's Cages for use by the Plaintiffs and the Plaintiffs' physicians. As such, each of the Medtronic Defendants is individually, as well as jointly and severally, liable to the Plaintiffs for the Plaintiffs' damages.

833. The conduct of the Defendants herein caused the Plaintiffs' harm as described herein. The Plaintiffs' harm is not in any way attributable to any fault of the Plaintiffs'. Uncertainty may exist regarding which Defendant(s) and/or combination of Defendants caused the Plaintiffs' harm. The Defendants possess superior knowledge and information regarding which Defendant(s) and/or combination of Defendants caused the Plaintiffs' injuries. Thus, the burden of proof is upon each Defendant to prove the Defendant did not cause the Plaintiffs' harm as described herein.

834. Due to the above, each Cause of Action named below is asserted against each Defendant herein, jointly and severally, even if each and every Defendant herein is not specifically identified as to each and every count.

## IX. CLAIMS FOR RELIEF

### FIRST CAUSE OF ACTION
### Fraudulent Concealment, Misrepresentation and Fraud

835. Plaintiffs incorporate by reference all previous and subsequent paragraphs of this Complaint as if fully set forth herein and further allege as follows:

836. These Defendants had a confidential and special relationship with Plaintiffs and/or their physicians due to (a) Defendants' vastly superior knowledge of the health and safety risks relating to Infuse®, the BMP/Sponge and P's Cages; and (b) Defendants' sole and/or superior knowledge of their dangerous and irresponsible practices of improperly promoting the off-label use of Infuse®, the BMP/Sponge and P's Cages.

837. These Defendants and their KOL's knew of many or all of the risks eventually revealed in the June, 2011 issue of *The Spine Journal* and then again confirmed by the YODA studies.

838. Defendants had an affirmative duty to fully and adequately warn Plaintiffs and their physicians of the true health and safety risks associated with the BMP/Sponge and P's Cages for the uses intended by these Defendants; namely, for posterior approach spine fusion surgery using Class II surgical cages unapproved for use with a biologic, like BMP.

839. Defendants also had a duty to disclose their dangerous and irresponsible practices of improperly promoting to physicians, such as Plaintiffs' Surgeons, the off-label use of the BMP/Sponge and/or P's Cages.

840. Independent of any special relationship of confidence or trust, Defendants had a duty not to conceal the risks associated with using the BMP/Sponge and/or P's Cages from Plaintiffs and/or their physicians. Instead, under state common law, these Defendants had a duty to fully disclose such risks and dangers to Plaintiffs and/or their physicians.

841. The Medtronic Defendants fraudulently and intentionally misrepresented and/or fraudulently concealed material and important health and safety product risk information from Plaintiffs and their physicians, all as alleged in this Complaint.

842. Plaintiffs and/or their physicians would not have decided to use the BMP/Sponge and/or P's Cages had they known of the true safety risks related to such use, all of which were known to the Medtronic Defendants.

843. Any of the following is sufficient to independently establish these Defendants' liability for fraudulent misrepresentation, fraudulent concealment and/or fraud in the inducement:

a. The Medtronic Defendants fraudulently concealed and/or misrepresented the health and safety hazards, symptoms, diseases and/or health problems associated with the BMP/Sponge and/or P's Cages for the purposes intended by these Defendants;

b. The Medtronic Defendants fraudulently concealed and/or misrepresented their illegal, improper and unethical schemes to promote and market the off-label, unapproved and experimental use of the BMP/Sponge and/or P's Cages as detailed in the factual allegations of this Complaint;

c. The Medtronic Defendants fraudulently concealed and/or misrepresented their illegal, improper and unethical participation in drafting many of the clinical studies published by their KOLs. Unsuspecting physicians, including Plaintiffs' Surgeons, justifiably relied on such studies regarding the risk and benefit of the BMP/Sponge and/or P's Cages in treating patients, like Plaintiffs herein, for the uses and in the manner intended by these Defendants;

d. The Medtronic Defendants, as described above, fraudulently concealed and/or misrepresented information about the known comparative risks and benefits of the use of the BMP/Sponge and P's Cages and the relative benefits and availability of alternate products, treatments and/or therapies;

e. The Medtronic Defendants failed to disclose the conflicts of interest and biases created by these Defendants' large payments to their KOLs, who advocated off-label use through Continuing Medical Education ("CME") efforts, lectures, dinner meeting and published articles and studies purporting to be "objective" scientific information; and,

f. The Medtronic Defendants engaged in the systematic off-label promotion and misrepresentations as described in Section IV.K above and in other Sections this Complaint.

844. The Medtronic Defendants knew that they were concealing and/or misrepresenting true information about the comparative risks and benefits of the use of the BMP/Sponge and/or P's Cages and the relative benefits and availability of alternate products, treatments and/or therapies.

845. The Medtronic Defendants knew that Plaintiffs and their physicians would regard the matters Defendants concealed and/or misrepresented to be important in determining the course of treatment for Plaintiffs, including Plaintiffs and their physicians' decision whether to use the BMP/Sponge and/or P's Cages for the purposes and in the manner intended by these Defendants.

846. The Medtronic Defendants intended to cause Plaintiffs and their physicians to rely on their concealment of information and/or misrepresentations about the safety risks related to the BMP/Sponge and P's Cages to induce them to make off-label and unapproved use of Infuse® and its components.

847. Plaintiffs and/or their physicians were justified in relying, and did rely, on Defendants' concealment of information and/or misrepresentations about the safety risks related to the BMP/Sponge and/or P's Cages in deciding to use these devices in Plaintiffs' spine fusion surgeries.

848. As the direct, proximate and legal cause and result of the Defendants' fraudulent concealment and misrepresentations and suppression of material health and safety risks relating the BMP/Sponge and/or P's Cages and Defendants' dangerous and irresponsible marketing and promotion practices, Plaintiffs have been injured and has incurred damages, including but not limited to medical and hospital expenses, lost wages and lost earning capacity, physical and mental pain and suffering, and loss of the enjoyment of life.

849. Plaintiffs are therefore entitled to damages in an amount to be proven at trial, together with interest thereon and costs.

**SECOND CAUSE OF ACTION**
**Failure to Warn**

850. Plaintiffs incorporate by reference all previous and subsequent paragraphs of this Complaint as if fully set forth herein and further allege as follows:

851. The Medtronic Defendants had a duty to warn Plaintiffs and their physicians about the risks and benefits of the BMP/Sponge and/or P's Cages of which they knew, or in the exercise of ordinary care, should have known, at the time the BMP/Sponge and/or P's Cages left the Defendants' control.

852. Specifically, these Defendants, through their employees and agents, including but not limited to sales representatives, had a duty to warn of the specific risks and benefits they knew or should have known of using the BMP/Sponge and/or P's Cages for the purposes these Defendants intended; namely, for posterior approach spine fusion surgery with a Class II cage unapproved for use with a biologic, like BMP.

853. These Defendants should have known of such risks and benefits as detailed in the June, 2011 issue of *The Spine Journal* and also revealed in the YODA study, had they performed adequate and unbiased clinical testing of these unapproved, experimental medical devices, as they had a duty to do.

854. Any warning given by the Medtronic Defendants to Plaintiffs and/or to Plaintiffs' Surgeons was rendered inadequate due to the illegal, improper and/or false promotion, by such Defendants, of the off-label use of the BMP/Sponge and P's Cages.

855. As detailed in Count I above, these Defendants likely did know of many or all such risks and benefits, and yet failed to disclose them or simply misrepresented the risks and the benefits.

856. The Medtronic Defendants did know, or should have known, of the dangers of the misuse of a Class II device in combination with a biologic, such as BMP.

857. These Defendants breached their duty by failing to warn Plaintiffs and their physicians of the specific risks and benefits of using their medical devices.

858. Defendants, each of them, knew that the BMP/Sponge and P's Cages would be purchased, resold and used by the hospital and Plaintiffs' surgeons without inspection or adequate investigation for defects in the design of the product for the purposes Medtronic intended them to be used and in the manner they were used, which defects rendered these products, as sold to and used by Plaintiffs, unreasonably dangerous.

859. The warnings and instructions accompanying the BMP/Sponge failed to provide the level of information that an ordinarily prudent physician or consumer would expect when using the product in such a reasonably foreseeable manner.

860. The Medtronic Defendants either recklessly or intentionally minimized and/or downplayed the risks of serious side effects related to use of the BMP/Sponge and/or P's Cages, and exaggerated the benefits related to such use.

861. Plaintiffs and their physicians would not have used the BMP/Sponge and/or P's Cages had they known of the true safety risks related to their use.

862. As a direct and proximate result of one or more of the above-listed dangerous conditions, defects and negligence, Plaintiffs sustained serious injuries of a personal and pecuniary nature from the date of their spine fusion surgeries to the present.

863. Plaintiffs are therefore entitled to damages in an amount to be proven at trial, together with interest thereon and costs.

**THIRD CAUSE OF ACTION**
**Strict Products Liability – Design Defect**

864. Plaintiffs incorporate by reference all previous and subsequent paragraphs of this Complaint as if fully set forth herein and further allege as follows:

865. As displayed through their actions, words and other objective information, these Defendants intended the BMP/Sponge and/or P's Cages to be used in an off-label, unapproved and experimental manner in spine fusion surgery (that is, without an LT-Cage™ in a cage not approved by the FDA as a Class III device, and by placing it through a medial, lateral and/or other posterior surgical approach), thus creating an entirely new combination medical device which had not been subjected to adequate pre-clinical or clinical testing or FDA review and approval; thus, the BMP/Sponge and/or P's Cages implanted in Plaintiffs was an experimental device, and was for that reason and others, unreasonably dangerous.

866. The device, as intended by these Defendants, reached Plaintiffs without a substantial change in the condition in which it was sold.

867. Defendants' device, a combination of the BMP/Sponge and/or P's cages, was defectively designed because the design was unsafe for the purposes intended by the Medtronic Defendants, in the manner promoted by such Defendants and/or in a manner reasonably foreseeable by Defendants.

868. Defendants' Class II devices used in Plaintiffs' surgeries were defectively designed because the design was unsafe when used off-label in the manner promoted by Defendants and/or in a manner reasonably foreseeable by Defendants.

869. The BMP/Sponge and/or P's Cages, for the uses intended by these Defendants, failed to perform as safely as an ordinary consumer would expect when used in the manner intended and marketed by them. The risks of these devices outweighed their benefits when used for the purposes and in the manner intended and foreseeable by these Defendants

870. These devices were designed in a way that caused users to suffer injuries including, but not limited to, pain and weakness in limbs, radiculitis, ectopic bone formation, osteolysis, and poorer global outcomes than equally-effective, alternative designs and treatments.

871. These foreseeable risks of harm could have been reduced or avoided by adopting a reasonable alternative design, as originally approved by the FDA. However, Defendants did not adopt a design that would have rendered the components of the Infuse® product reasonably safe.

872. Plaintiffs and their physicians used these devices in a manner intended and reasonably foreseeable by Defendants.

873. Plaintiffs and their physicians were not aware of the aforementioned defects at any time prior to the injuries caused by these devices.

874. As a legal and proximate result of the aforementioned defects, Plaintiffs have sustained the injuries and damages set forth herein.

875. Plaintiffs are therefore entitled to damages in an amount to be proven at trial, together with interest thereon and costs.

## FOURTH CAUSE OF ACTION
**Negligent Misrepresentation**

876. Plaintiffs incorporate by reference all previous and subsequent paragraphs of this Complaint as if fully set forth herein and further allege as follows:

877. At all relevant times, Defendants were engaged in the business of selling the BMP/Sponge and/or P's Cages for resale or use, and in fact did sell these devices used by Plaintiffs' implanting surgeons to the hospital, which then resold it to Plaintiffs.

878. Specific defects in these products, as specified above in this Complaint, rendered them defective and unreasonably dangerous.

879. In the course of marketing these products, the Defendants made untrue representations of material facts and/or omitted material information to Plaintiffs, their physicians, and the public at large.

880. Plaintiffs and/or their physicians reasonably relied on such misrepresentations and/or omissions and were thereby induced to purchase these products.

881. Plaintiffs and their physicians would not have purchased and used these products had they known of the true safety risks related to such use.

882. Defendants were negligent in making these untrue misrepresentations and/or omitting material information because Defendants knew, or had reason to know, of the actual, unreasonable dangers and defects in their products.

883. Plaintiffs and their physicians were justified in relying, and did rely, on the misrepresentations and omissions about the safety risks related to Defendants' products.

884. As the direct, producing, proximate and legal result of the Defendants' misrepresentations, Plaintiffs have suffered severe physical pain, medical and hospital expenses, lost wages, pain and suffering, and pecuniary loss.

885. Plaintiffs are therefore entitled to damages in an amount to be proven at trial, together with interest thereon and costs.

**FIFTH CAUSE OF ACTION**
**Product Liability--Negligence**

886. Plaintiffs incorporate by reference all previous and subsequent paragraphs of this Complaint as if fully set forth herein and further allege as follows:

887. Defendants marketed the BMP/Sponge and/or P's Cages to and for the benefit of Plaintiffs.

888. Defendants owed Plaintiffs, and their physicians, duties to exercise reasonable or ordinary care under the circumstances in light of the generally recognized and prevailing scientific knowledge at the time the product was sold.

889. Through the conduct described in the foregoing paragraphs of this Complaint, Defendants breached their duties to Plaintiffs and to their physicians.

890. Defendants knew, or should have known, that, due to their failure to use reasonable care, Plaintiffs and their physicians would use and did use their products to the detriment of Plaintiffs' health, safety and well-being.

891. As the direct, producing, proximate and legal result of the Defendants' negligence, Plaintiffs have suffered severe physical pain, medical and hospital expenses, lost wages, pain and suffering, and pecuniary loss.

892. Plaintiffs are therefore entitled to damages in an amount to be proven at trial, together with interest thereon and costs.

**SIXTH CAUSE OF ACTION**
**Breach of Express Warranty**

893. Plaintiffs repeat and incorporate by reference all other paragraphs of this Complaint as if fully set forth herein and further allege as follows:

894. The Medtronic Defendants utilized journal articles, advertising media, sales representatives, and paid Key Opinion Leaders (KOLs) to promote, encourage, and urge the use, purchase, and utilization of the BMP/Sponge and/or P's Cages by representing the quality to health care professionals, Plaintiffs, and the public in such a way as to induce its purchase or use.

895. Through these representations, the Medtronic Defendants made an express warranty that the BMP/Sponge and/or P's Cages would conform to the representations. More specifically, Medtronic represented that the BMP/Sponge when used with P's Cages, and other surgical cages like them, or without a cage at all, was safe and effective, that it was safe and effective for use by individuals such as Plaintiffs, and/or that it was safe and effective to treat their condition.

896. The Medtronic Defendants manipulated studies, crafted by both lucratively paid physicians and their agents/employees, as promotional materials, which created express written representations of the safety and efficacy of these devices including that adverse events related to the use of the BMP Sponge in combination with such surgical cages did not exist or were significantly reduced. These specific misrepresentations went beyond mere puffery as they were published in reputable peer-reviewed scientific journals.

897. The representations, as set forth above, contained or constituted affirmations of fact or promises made by the seller to the buyer which related to the goods and became part of the basis of the bargain creating an express warranty that the goods shall conform to the affirmations of fact or promises.

898. Plaintiffs did not conform to the representations made by the Medtronic Defendants, because these devices were not safe and effective, were not safe and effective for

use by individuals such as Plaintiffs, and/or was not safe and effective to treat in individuals, such as Plaintiffs for the uses and the manner intended by these Defendants.

899. At all relevant times, Plaintiffs used these devices for the purpose and in the manner intended by the Medtronic Defendants.

900. Plaintiffs and Plaintiffs' physicians, by the use of reasonable care, could not have discovered the breached warranty and realized its hidden increased risks and it unreasonable dangers.

901. Defendants' breaches constitute violations of state common laws.

902. The breach of the warranty was a substantial factor in bringing about Plaintiffs' severe and debilitating injuries, economic loss, and other damages, including but not limited to, cost of medical care, rehabilitation, lost income, ectopic bone growth, inflammatory reaction, non-union, cancer, neuro deficit, nerve injury, and neurological injury, immobility, pain and suffering, and mental and emotional distress for which they are entitled to compensatory and equitable damages and declaratory relief in an amount to be proven at trial.

## SEVENTH CAUSE OF ACTION
**Breach of Implied Warranty**

903. Plaintiffs repeat and incorporate by reference all other paragraphs of this Complaint as if fully set forth herein and further allege as follows:

904. The BMP/Sponge and/or P's Cages were not reasonably fit for the ordinary purposes for which such goods are used and did not meet the expectations for the performance of the product when used in the customary, usual and reasonably foreseeable manner. Nor were these products minimally safe for their expected purpose.

905. At all relevant times, Plaintiffs used these products for the purpose and in the manner intended by the Medtronic Defendants.

906. The breach of the warranty was a substantial factor in bringing about Plaintiffs' injuries.

907. Defendants breached their implied warranty to Plaintiffs in that Medtronic's products were not of merchantable quality, safe and fit for their intended use, or adequately tested, in violation of State Common Law principles.

908. As a direct and proximate result of the Medtronic Defendants' acts and omissions, Plaintiffs were implanted with the BMP/Sponge and/or P's Cages and suffered severe and debilitating injuries, economic loss, and other damages, including but not limited to, cost of medical care, rehabilitation, lost income, ectopic bone growth, inflammatory reaction, non-union, neuro deficit, nerve injury, neurological injury, pain and suffering and great emotional and mental distress and anguish for which they are entitled to compensatory, special, and equitable damages in an amount to be proven at trial.

**ADDITIONAL ALLEGATIONS REGARDING CLAIM FOR PUNITIVE DAMAGES**

909. Plaintiffs incorporate by reference all previous and subsequent paragraphs of this Complaint as if fully set forth here and further allege as follows:

910. At all times herein referenced, officers, directors, and managing agents of all or some of the Defendants herein knew, and were aware, and concealed, hid, and/or otherwise downplayed (or were in the alternative recklessly unaware of) the true risks of the off-label and unapproved uses of Infuse® and its components.

911. At all times herein referenced, officers, directors, and managing agents of such Defendants knew, and were aware, or were grossly negligent and reckless in not being aware, that numerous people had ectopic bone formation, radiculitis, osteolysis, cage migration, and

worse overall outcomes as a result of the using the BMP/Sponge in combination with surgical cages like P's Cages, for posterior approach spine fusion surgeries.

912. Such Defendants, some or all, designed, engineered, developed, manufactured, fabricated, assembled, equipped, tested or failed to test, inspected or failed to inspect, labeled, advertised, promoted, marketed, supplied, distributed, wholesaled, and/or otherwise sold the BMP/Sponge and/or cages like P's Cages sold the Plaintiffs herein, when they knew, or should have known, or were recklessly unaware, that these products were dangerous and unsafe for the purpose for which they intended it to be used, namely, as an unapproved bio-engineering bone draft device in "off-label" spinal fusion surgeries.

913. Further, at all times, some or all of the Defendants knew, or recklessly should have known, that that these products had caused serious injuries and damage to other members of the public.

914. At all times herein mentioned, some of all of the Defendants intentionally suppressed the aforementioned complaints, actively concealed and downplayed the risks associated with these products, actively promoted the illegal, off-label use these products, failed to warn Plaintiffs and the medical community of the true risks associated with these products and saturated the scientific and medical literature with biased, industry-funded studies to conceal the true risks of these products, and otherwise failed to warn Plaintiffs, the medical community, and/or the general public.

915. At all times herein mentioned, some or all of the Defendants had actual knowledge of the facts hereinabove alleged demonstrating that serious injury to patients in which the BMP component of Infuse® was implanted, particularly in an off-label, unapproved manner such as in the spine fusion procedures Plaintiffs underwent. Defendants nevertheless

deliberately suppressed, concealed, downplayed, and/or otherwise hid any information demonstrating the true risks associated with these products from Plaintiffs, the medical community, and/or the general public. Instead, such Defendants continued to actively promote the use of these products in an effort to maintain enormous profitability, at the expense of great injury to thousands of individuals, like Plaintiffs.

916. As a legal and proximate result of Defendants' conduct, as herein alleged, Plaintiffs have sustained the injuries and damages set forth above.

917. Plaintiffs are therefore entitled to exemplary or punitive damages, which would serve to punish the Defendants and to deter wrongful conduct in the future.

918. Plaintiffs are therefore entitled to judgment against Defendants as hereinafter set forth.

**PRAYER FOR RELIEF**

WHEREFORE, Plaintiffs request of this Court the following relief:

A. For general damages, in an amount exceeding the jurisdictional limits of this Court and the diversity jurisdictional limits of the U. S. District Court to be proven at trial;

B. For past and future medical, incidental, hospital, psychological care and other expenses, in an amount to be proven at the time of trial;

C. For past and future loss of earnings and destruction of earning capacity, in an amount to be proven at the time of trial;

D. For past and future mental, emotional, and physical pain and suffering, in an amount to be proven at the time of trial;

E. For an award of pre-judgment and post-judgment interest as provided by law;

F. For consequential damages, in an amount to be proven at the time of trial;

G. For exemplary or punitive damages against the Medtronic Defendants;

H. For an award providing for payment of costs of suit;

I. A trial by jury;

J. For Plaintiffs' costs herein expended; and

K. For such other and further relief as this Court may deem just and proper.

Dated: April 28, 2014

Respectfully submitted,

*/s/ Leslie M. Cronen*

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**CERTIFICATE OF SERVICE**

I hereby certify that on April 28, 2014, the foregoing was electronically filed with the Clerk of the Court using the CM/ECF system, which will send notification to the attorneys of record in this matter who are registered with the Court's CM/ECF system.

*/s/Leslie M. Cronen*
*Counsel for Plaintiff*